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PHOTO-ELASTIC BEHAVIOUR OF CUBIC CRYSTALS

New Methods of Distinguishing Between Different Classes

By S. Bhagavantam, F.A.Sc.

(From the Physical Laboratories, Osmania University, Hyderabad)

Received April 20, 1953

1. Introduction

By the application of group theoretical methods, the author has shown (1942) that the T and T_h classes of the cubic system of crystals should behave differently from the T_d, O and O_h classes in respect of their photo-elastic properties. The main conclusion was that in the former cases, there should exist a fourth photo-elastic constant whereas the maximum number permissible in the T_d, O and O_h classes is only three. Since then, this has been verified by direct measurements in potassium and ammonium alums, in barium and lead nitrates and in sodium chlorate by different investigators. The subject has attracted considerable attention and several interesting results, not contemplated in the schemes given earlier by Pockels and covering crystal systems other than the cubic as well, have been derived by Fumi (1952). A slightly different and interesting result that a simple compressional stress will under certain conditions result in the axis of stress and a line perpendicular thereto not remaining the principal optical directions in the C_3, C_{3h}, C_6, etc., classes was obtained and pointed out by the author (1952). This has led the author to examine the cubic crystals in detail once again and many new conclusions are now drawn. Some of them, as will be seen in the following sections, furnish easy and simple means of distinguishing between the T and T_h classes on the one hand and the T_d, O and O_h on the other.

2. Photo-Elastic Behaviour of Cubic Crystal Prisms

In earlier investigations on the subject, explicit schemes have been given for all the cubic classes and they will not be repeated here. The T and T_h differ from T_d, O and O_h because, in them $q_{12} \neq q_{13}$. All these differ from isotropic glasses because, in them $q_{11} - q_{12} \neq q_{44}$. The prisms that are generally prepared and used are of three kinds, the edges in each case being parallel to [001], [100], [010]; [001], [110], [$\bar{1}$10] and [111], [$\bar{2}$11], [01$\bar{1}$] respectively. For convenience, the square brackets will be omitted hereafter. Results for these three prisms are worked out and given in the

following table. Details follow the usual methods and it is not necessary to reproduce them here. Some of these cases have been worked out earlier (Suryanarayana, 1948; Ramachandran and Chandrasekharan, 1951) but not all. θ in the following table stands for the angular displacement of the principal axes with reference to the stress direction and $A = q_{11} - q_{12}/2 - q_{13}/2$.

TABLE I

Prism No.	Serial No.	Direction of pressure	Direction of observation	Birefringence proportional to	Tilt of axes Tan 2θ	Condition for $2\theta = 0$
I	1	001	100	$q_{11}-q_{12}$	0	..
	2	,,	010	$q_{11}-q_{13}$	0	
	3	100	001	$q_{11}-q_{12}$	0	..
	4	,,	010	$q_{11}-r_{13}$	0	
	5	010	100	$q_{11}-q_{12}$	0	..
	6	,,	001	$q_{11}-q_{13}$	0	
II	7	001	110	A	0	..
	8	,,	$\bar{1}10$	A	0	
	9	110	001	$\frac{1}{2}\sqrt{4q_{44}^2+1(q_{12}-q_{13})^2}$	$\frac{q_{12}-q_{13}}{2q_{44}}$	$q_{12}=q_{13}$
	10	,,	$\bar{1}10$	$\frac{1}{2}A+\frac{1}{2}q_{44}$	0	..
	11	$\bar{1}10$	001	$\frac{1}{2}\sqrt{4q_{44}^2+(q_{12}-q_{13})^2}$	$\frac{q_{12}-q_{13}}{2q_{44}}$	$q_{12}=q_{13}$
	12	,,	110	$\frac{1}{2}A+\frac{1}{2}q_{44}$	0	..
III	13	111	$\bar{2}11$	q_{44}	0	..
	14	,,	$01\bar{1}$	q_{44}	0	..
	15	$\bar{2}11$	111	$\frac{1}{3}\sqrt{(A+2q_{44})^2+\frac{1}{3}(q_{12}-q_{13})^2}$	$\frac{\sqrt{3}}{2}\cdot\frac{q_{12}-q_{13}}{A+2q_{44}}$	$q_{12}=q_{13}$
	16	,,	$01\bar{1}$	$\frac{1}{3}\sqrt{\frac{1}{2}(A+5q_{44})^2+2(A-q_{44})^2}$	$\frac{2\sqrt{2}(A-q_{44})}{A+5q_{44}}$	$A=q_{44}$
	17	$01\bar{1}$	$\bar{2}11$	$\frac{1}{6}\sqrt{(A+5q_{44})^2+6(q_{12}-q_{13})^2}$	$\frac{\sqrt{6}(q_{12}-q_{13})}{A+5q_{44}}$	$q_{12}=q_{13}$
	18	,,	111	$\frac{1}{3}\sqrt{(A+2q_{44})^2+\frac{1}{3}(q_{12}-q_{13})^2}$	$\frac{\sqrt{3}}{2}\cdot\frac{q_{12}-q_{13}}{A+2q_{44}}$	$q_{12}=q_{13}$

Results contained in the above table are comprehensive and in some instances furnish easy methods of distinguishing between different classes of cubic crystals.

3. Discussion of Results

Cases covered by serial Nos. 9, 11, 15, 17 and 18 are noteworthy as they indicate that in all these instances, we should expect an angular displacement of the principal axes by the application of a simple compressional stress in the appropriate direction because of the circumstance $q_{12} \neq q_{13}$ in the T and T_h classes. Since $q_{12} = q_{13}$ in the T_d, O and O_h classes, no such result is expected. This furnishes a much simpler method of experimentally verifying the validity of the schemes given by the author (1942) for the photo-elastic behaviour of T and T_h classes as against the schemes given by Pockels. The experiment merely consists in compressing either the prism II or III in the appropriate direction, namely 110 or $\bar{1}10$ in the first case and 211 or $01\bar{1}$ in the second, and observing the rotation of the principal axes in a section perpendicular to the direction of observation. This is easily done by locating the prism between a pair of crossed nicols. If $q_{12} = q_{13}$, we should find no rotation and so no restoration of light in any of these cases. On the other hand, every one of these cases has been examined recently in the author's laboratory and the angular displacement measured for quite a few crytsals and the results are compared in a following paper with the figures that are expected. That there is such a rotation in case No. 9 for sodium chlorate crystals has been recognised by Ramachandran and Chandrasekharan (1951) but the expression given by them for tan 2θ is the inverse of what is obtained here.

Case No. 16 is unique and stands on a different footing from all other cases. This tells us that even if $q_{12} = q_{13}$, we should expect a rotation provided $q_{11} - q_{12} \neq q_{44}$ as is the case in T_d, O and O_h classes. Thus by cutting a prism $\bar{2}11$, 111, $01\bar{1}$ from a cubic crystal belonging to any one of the five classes, we should expect to observe the phenomenon provided the compression is along $\bar{2}11$ and the observation along $01\bar{1}$. Ramachandran (1947) has noticed the effect while working with diamond precisely for this orientation. It is interesting to note that of all the 18 possibilities studied in the present paper, this is the only orientation where such a phenomenon can be expected for all classes of cubic crystals. The effect vanishes as we pass from cubic crystals to isotropic glasses because, in them $q_{11} - q_{12} = q_{44}$ and may be regarded as a feature which distinguishes the former from the latter in respect of their photo-elastic behaviour.

4. Summary and Conclusion

The photo-elastic behaviour of chosen prisms belonging to different classes of the cubic system of crystals is studied in detail for various orientations. It is shown that five out of the eighteen orientations studied furnish

a simple experimental test for distinguishing the T and T_h classes from th T_d, O and O_h classes. In the former, on account of the fact that $q_{12} \neq q_{13}$, there is an angular displacement of the principal axes of certain sections of the optical ellipsoid, caused by the application of linear compressional stresses and such an effect may easily be observed and measured. It has also been shown that there is one special orientation for which all the five classes of cubic crystals should exhibit such an effect because $q_{11} - q_{12} \neq q_{44}$. This vanishes for isotropic substances as should be expected.

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PHOTO-ELASTIC BEHAVIOUR OF CUBIC CRYSTALS

Displacement of Principal Axes Caused by Linear Stresses

By S. Bhagavantam, F.A.Sc. and K V. Krishna Rao
(From the Physical Laboratories, Osmania University, Hyderabad)

Received April 20, 1953

1. Introduction

In a previous paper by one of us (1953), it has been shown that linear stresses will cause the principal axes of certain sections of the optical ellipsoid to be tilted and it was pointed out that this effect may be used for distinguishing the T and T_h classes of crystals from the T_d, O and O_h ones in the cubic system. The results of experiments conducted by us with barium and lead nitrates (T_h class), ammonium and potassium alums (T_h class) and fluorite (O_h class) are given in this paper. In all these cases, except lead nitrate, prisms already cut and prepared by Suryanarayana (1948) in this laboratory have been used. Crystals of lead nitrate are freshly grown and prisms are now prepared for the purpose of these studies. The photo-elastic constants assumed and used in calculating the θ values as per formulæ given in the preceding paper already referred to (1953) are given in Table I. In Table II, the measured values of θ are compared with the calculated ones.

2. Method of Measurement

In all cases, the appropriate prism is held between two crossed nicols mounted on graduated circles. The prism is subjected to a linear compressional stress along one of its axes, the vertical one in practice. The direction of observation is horizontal and perpendicular to the stress direction. If there is a tilt of the principal axes in the section perpendicular to the direction of observation, the reference line being the stress direction, restoration of light is immediately noticed and the tilt may be measured by suitably rotating the pair of crossed nicols to a new position of extinction. In individual cases, several readings are taken and the averages arrived at but the angles given in Table II may be taken generally as good enough only to a degree. In some, where the prisms are small and the observation difficult, errors are larger.

3. RESULTS

TABLE I

Photo-Elastic Constants

	Barium nitrate	Lead nitrate	Ammonium alum	Potassium alum	Fluorite
$-(q_{11}-q_{12})$ ..	23·84	19·13	5·93	5·21	1·45
$-(q_{11}-q_{13})$ ..	17·13	11·84	5·25	4·64	,,
$-q_{44}$ ..	1·69	1·39	1·15	0·63	−0·70

Units of 10^{-13} C.G.S.

TABLE II

Angular Tilts

Description of the measurement	Barium nitrate		Lead nitrate		Ammonium alum		Potassium alum		Fluorite	
	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.
Stress along $[\bar{2}11]$ Obs. along $[0\bar{1}1]$	29°	30° 43′	26°	30° 18′	25°	23° 57′	26°	28° 12′	38°	35° 40′
Stress along $[\bar{2}11]$ Obs. along $[111]$	11°	6° 51′	6°	9° 32′	4°	2° 8′	3°	2° 17′	..	..
Stress along $[0\bar{1}1]$ Obs. along $[111]$	11°	6° 51′	7°	9° 32′	4°	2° 8′	4°	2° 17′	..	..
Stress along $[0\bar{1}1]$ Obs. along $[\bar{2}11]$	12°	14° 48′	17°	19° 15′	6°	4° 11′	5°	4° 55′	0	0
Stress along $[\bar{1}10]$ Obs. along $[001]$	30°	31° 38′	30°	34° 34′	13°	8° 15′	8°	12° 10′	..	..
Stress along $[\bar{1}10]$ Obs. along $[001]$	34°	31° 38′	32°	34° 34′	4°	8° 15′	0°	12° 10′	..	..

4. Discussion of Results

The notable features of Table II are that even fluorite which belongs to the O_h class shows the effect in one case, as should be expected, and the measured angle agrees with the calculated one (first row). In other cases as well, the agreement between the observed and calculated values is fair. All orientations, except the one contained in the first row, serve to distinguish between the T and T_h classes on the one hand and the T_d, O and O_h on the other. The distinction is clear-cut, easy to observe and to measure. In certain cases, for example the second and third rows, the calculated effect is the same in magnitude and this is a result of the symmetry. Observed values confirm this conclusion to a fair degree of accuracy in several cases. Similar remarks apply to the fifth and the sixth rows.

5. Summary

The paper furnishes measurements in respect of the tilts observed of the principal axes in sections of the optical ellipsoid caused by linear stresses applied to prisms cut out of different cubic classes of crystals. In most cases, such effects are characteristic only of the T and T_h classes and are absent in the T_d, O and O_h classes. They serve, therefore, to distinguish between the two types. There is a fair agreement between the measured and calculated values in practically all the cases studied.

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PARTIAL METHYL ETHERS OF POLYHYDROXY COUMARINS

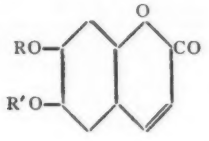
Part I. Partial Methylation of 5 : 7-Dihydroxy-4-Methyl Coumarin

By P. L. Sawhney and T. R. Seshadri, F.A.Sc.

(*From the Department of Chemistry, University of Delhi*)

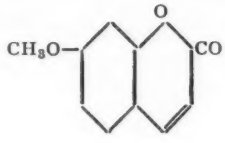
Received October 24, 1952

The possibility of obtaining partial methyl ethers of polyhydroxy coumarins by direct methylation would at first sight seem to be slender. No position of the coumarin structure seems to offer protection to a hydroxyl group just like the 5-position in chromones and flavones by a process of chelation. However, some instances are met with in the literature where coumarins have been successfully subjected to partial methylation. For example, Tiemann and Will[1] obtained a monomethyl ether by methylating æsculetin (I *a*) with methyl iodide and methyl alcoholic potash. Its constitution was not settled by them but the substance was different from scopoletin, a naturally occurring monomethyl ether of æsculetin. Moore[2] showed that scopoletin was the 6-methyl ether (I *b*) of æsculetin and hence Tiemann and Will's synthetic product should be the 7-methyl ether (I *c*). Its constitution was further established by Bargellini and Monti[3] who showed its identity with the nuclear oxidation product of umbelliferone methyl ether (II).



I

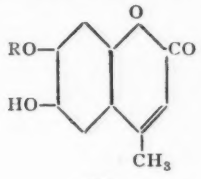
a, R = R' = H
b, R = H, R' = CH_3
c, R = CH_3, R' = H



II

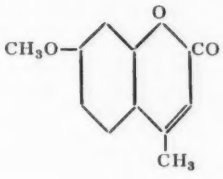
The partial methylation of 4-methyl æsculetin (III *a*) was carried out by Bargellini and Martegiani[4] using methyl iodide and methyl alcoholic potash at 100°. The constitution of the resulting monomethyl ether, m.p. 173–5°, was not settled and it was considered to be either the 6- or 7-monomethyl ether of 4-methyl æsculetin. No derivatives were described. Their product was probably impure because more recently Velluz and Amiard[5] carried out the partial methylation of 4-methyl æsculetin using dimethyl sulphate and aqueous sodium carbonate at 60° and obtained a monomethyl ether melting at 208–09°. They considered it to be 7-methoxy-6-hydroxy-4-methyl

coumarin (III *b*). The constitution should be considered to be correct based on the analogy of the methylation of æsculetin. It has been confirmed recently by Sawhney, Seshadri and Thiruvengadam[6] when this monomethyl ether was shown to be identical with the nuclear oxidation product of 4-methyl umbelliferone methyl ether (IV). It is therefore conclusively proved that the hydroxyl in the 7-position is markedly more easily methylated as compared to the 6-hydroxyl group.



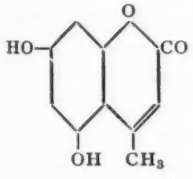
a, R=H
b, R=CH_3

III

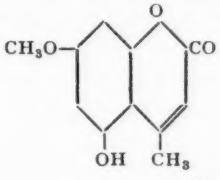


IV

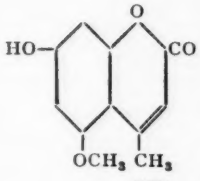
A similar report has been made by Schmid[7] of having carried out the partial methylation of 5: 7-dihydroxy-4-methyl coumarin (V) with diazomethane in methyl alcoholic solution and of having obtained a monomethyl ether. Using the analogy of æsculetin and 4-methyl æsculetin in which the 7-hydroxyl has greater reactivity (Merz and Hagemann[8]) he considered it to be 7-monomethyl ether (VI). His experiments prove the possibility of monomethylation of 5: 7-dihydroxy-4-methyl coumarin but do not definitely establish the position of the methoxyl group.



V



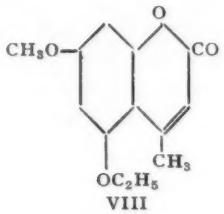
VI



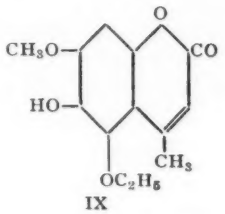
VII

Partial methylation of 5: 7-dihydroxy-4-methyl coumarin has now been carried out using dimethyl sulphate and aqueous sodium carbonate and the result is in agreement with that of Schmid.[7] The constitution of the partial methylation product has now been established in the following manner. The monomethyl ether of 5: 7-dihydroxy-4-methyl coumarin is ethylated and this methyl ethyl ether is subjected to nuclear oxidation by means of alkaline persulphate. As reported earlier[6] the oxidation of the *cis*-acid is not so satisfactory and preliminary conversion to the *trans*-acid is necessary for good yield. After nuclear oxidation, reconversion to the coumarin is effected in the presence of mercuric chloride as catalyst. The product

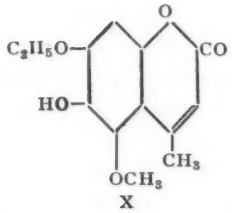
may have either of the constitutions (IX) or (X) depending on whether the monomethyl ether has the formula (VI) or (VII). This point has been settled by ethylating the oxidation product whereby is obtained a substance identical with 7-methoxy-5: 6-diethoxy-4-methyl coumarin (XI). This result conclusively proves the constitution of the methyl ethyl ether as (VIII) and the original monomethyl ether as (VI). It is therefore established that partial methylation of 5: 7-dihydroxy-4-methyl coumarin has taken place in the 7-position.



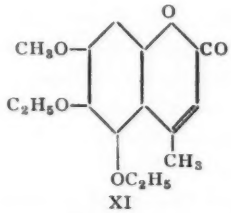
VIII



IX

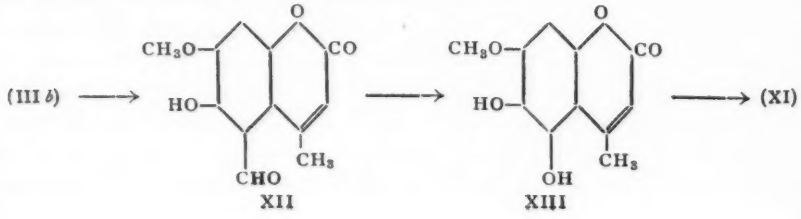


X

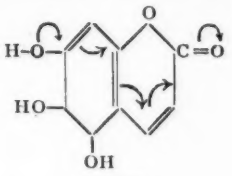


XI

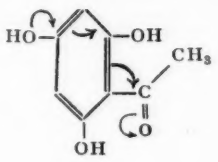
For the above comparison synthesis of 7-methoxy-5: 6-diethoxy-4-methyl coumarin (XI) has been made from 7-methoxy-6-hydroxy-4-methyl coumarin (III *b*) as follows. It is condensed with hexamine whereby the ortho-aldehyde (XII) is obtained. Subsequent Dakin's reaction yields 7-methoxy-5: 6-dihydroxy-4-methyl coumarin (XIII). The constitution of this substance is proved by complete methylation whereby the trimethyl ether is formed and found to be identical with 5: 6: 7-trimethoxy-4-methyl coumarin obtained by the methylation of 4-methyl fraxinol.[6] When the dihydroxy compound (XIII) is ethylated with excess of diethyl sulphate it yields 7-methoxy-5: 6-diethoxy-4-methyl coumarin (XI).



In seeking for an explanation of the success of partial methylation in the abovementioned cases of dihydroxy coumarins, as already mentioned, there is no possibility of partial protection. Obviously the factor involved is the higher reactivity of the 7-hydroxyl as compared with the others. This seems to be due to the effect of electromeric polarisation of the carbonyl group which is transmitted to the 7-position (*para*-position) effectively by the presence of conjugation. The 6-hydroxyl is not influenced in this way (XIV). Though the electromeric effect could be transmitted also to the 5-position (*ortho*-position) it cannot be obviously as strong as to the 7-position. There is analogy for this in the greater reactivity of the *para*-hydroxyl group in phloroacetophenone[9] (XV). In this connection may be mentioned the success of partial monomethylation in hydroxy isoflavones and flavanones involving the selective activation of the 7-hydroxyl group.[10]



XIV



XV

Experimental

7-Methoxy-6-hydroxy-4-methyl-coumarin-5-aldehyde (XII)

To an intimate mixture of 7-methoxy-6-hydroxy-4-methyl coumarin[5,6] (3 g.) and hexamine (6 g.) was added glacial acetic acid (25 c.c.) and the mixture heated in a boiling water-bath for 6 hours. The deep orange solution was hydrolysed by adding a boiling solution of hydrochloric acid (20 c.c. of concentrated hydrochloric acid and 20 c.c. of water). The mixture was left overnight and then distilled under reduced pressure. The residual pasty mass was diluted with water and repeatedly extracted with ether and the ether solution dried over calcium chloride. The aldehyde obtained by evaporating the ether solution was crystallised from ethyl alcohol when it came out as yellow rectangular prisms melting at 214–6°. Yield, 1·5 g. With alcoholic ferric chloride it gave a pale green colour changing to pinkish green (Found: C, 61·3; H, 4·5; $C_{12}H_{10}O_5$ requires C, 61·6 and H, 4·3%).

7-Methoxy-5: 6-dihydroxy-4-methyl coumarin (XIII)

The above hydroxy-aldehyde (1 g.) was dissolved in pyridine (10 c.c.) and sodium hydroxide solution (5 c.c., I N) was added. It was cooled in ice and hydrogen peroxide (1·5 c.c., 20%) was slowly added with shaking. After one hour it was acidified with cold dilute hydrochloric acid, filtered

and the filtrate repeatedly extracted with ether. The ethereal layer was successively washed with dilute hydrochloric acid and water and dried over anhydrous sodium sulphate. It was evaporated and the residue crystallised from methyl alcohol when it came out as colourless rectangular plates and prisms melting at 237–8°. Yield, 0·6 g. It gives a violet colour with ferric chloride (Found: C, 59·3; H, 4·6; $C_{11}H_{10}O_5$ requires C, 59·5 and H, 4·5%).

5: 6: 7-*Trimethoxy*-4-*methyl coumarin*

The above methoxy dihydroxy coumarin (0·5 g.) was refluxed in dry acetone (50 c.c.) with dimethyl sulphate (1 g.) and anhydrous potassium carbonate (3 g.) for 6 hours. The solution was filtered and the filtrate evaporated. The residue on crystallisation from ethyl acetate came out as thick rhombic plates melting at 113–4°. Mixed melting point with an authentic sample prepared by the methylation of 4-methyl fraxinol[6] was undepressed.

7-*Methoxy*-5-*hydroxy*-4-*methyl coumarin* (*VI*)

5: 7-Dihydroxy-4-methyl coumarin (5 g.) was dissolved in aqueous sodium carbonate (50 c.c., 10%). To this solution dimethyl sulphate (5 g.) was added and the mixture slowly heated with shaking in the course of half an hour to 60°. Shaking was continued for further half an hour without external heating and then the mixture allowed to stand for three hours at room temperature. The solid that separated out was collected and dissolved in aqueous sodium hydroxide (50 c.c., 5%). The alkaline solution was acidified and filtered. The residue was collected and crystallised from alcohol when it came out as colourless prismatic needles melting at 256–7°. Yield, 2·5 g. Schmid[7] reported 251–2° as its melting point.

On methylation with dimethyl sulphate and potassium carbonate in dry acetone it gave 5: 7-dimethoxy-4-methyl coumarin, m.p. 172–3°, identical with an authentic sample.

Its acetate was prepared using acetic anhydride and pyridine. On crystallisation from alcohol it was obtained as colourless rectangular plates melting at 189–90°. Schmid[7] gave 191° as the melting point for this compound.

7-*Methoxy*-5-*ethoxy*-4-*methyl coumarin* (*VIII*)

The above partial methylation product (3 g.) was ethylated by refluxing in dry acetone solution (200 c.c.) with diethyl sulphate (6 g.) and anhydrous potassium carbonate (15 g.) for 10 hours. The solution was filtered and the residue washed with hot acetone. The filtrate was evaporated and the product crystallised from methyl alcohol when it came out as colourless

elongated rectangular plates melting at 188–9°. Yield, 2·7 g. (Found: C, 67·0; H, 5·7; $C_{13}H_{14}O_4$ requires C, 66·7 and H, 6·0%).

7-Methoxy-5-ethoxy-6-hydroxy-4-methyl coumarin (IX)

(*a*) *Direct oxidation of 7-methoxy-5-ethoxy-4-methyl coumarin.*—Methoxy-ethoxy coumarin from the previous experiment (2 g.) was dissolved in aqueous sodium hydroxide (50 c.c., 10%) by heating and also adding pyridine (10 c.c.). A saturated solution of potassium persulphate (5 g.) was added drop by drop to the above solution, cooled in ice-water and with constant stirring, during 5 hours. The solution was allowed to stand for 24 hours, and just acidified (congo-red) when the original substance separated out (0·5 g.). It was filtered and the filtrate was twice extracted with ether to remove the last traces of the unchanged substance. The aqueous layer was treated with sodium bisulphite (1 g.) and concentrated hydrochloric acid (20 c.c.) and heated at 70–80° for half an hour. The solution was cooled, filtered and the filtrate extracted with ether. The ethereal solution was dried over anhydrous sodium sulphate and evaporated. The residue crystallised from methyl alcohol to give colourless stout prisms, m.p. 201–2°. Yield, 0·2 g. (Found: C, 62·5; H, 5·4; $C_{13}H_{14}O_5$ requires C, 62·4 and H, 5·6%).

(*b*) *Oxidation through the coumaric acid.*—7-Methoxy-5-ethoxy-4-methyl coumarin (2 g.) was dissolved in pyridine (20 c.c.), aqueous sodium hydroxide (50 c.c., 10%) and yellow mercuric oxide (1 g.) added to it. This was shaken vigorously for 2 hours, filtered and the filtrate directly treated with a saturated solution of potassium persulphate (5 g.), added dropwise and with constant mechanical stirring and cooling in ice-water for 6 hours. After 24 hours the solution was saturated with hydrogen sulphide and then acidified with concentrated hydrochloric acid (congo-red). The solid that separated out was filtered and the filtrate extracted with ether, to remove the original compound. Concentrated hydrochloric acid (30 c.c.) and sodium bisulphite (1 g.) were added to the aqueous solution and heated at 70–80° for half an hour. It was cooled and shaken with mercuric chloride (0·5 g.) for 15 minutes. The mixture was filtered and the filtrate extracted with ether. The ethereal extract was dried over anhydrous sodium sulphate and then evaporated. The residue was crystallised from alcohol and then from ethyl acetate when it came out as colourless prisms melting at 201–2°. Yield, 0·35 g. Mixed melting point with the sample described in the above experiment was undepressed.

7-Methoxy-5: 6-diethoxy-4-methyl coumarin (XI)

(*a*) *From 7-methoxy-5: 6-dihydroxy-4-methyl coumarin.*—7-Methoxy-5: 6 dihydroxy-4-methyl coumarin (1·0 g.) was dissolved in dry acetone (100 c.c.)

diethyl sulphate (2 g.) and anhydrous potassium carbonate (10 g.) added and the solution refluxed for 10 hours. It was filtered and the filtrate evaporated. The residue was crystallised from methyl alcohol when it came out as long flat needles melting at 168–9° (Found: C, 64·7; H, 6·5; $C_{15}H_{18}O_5$ requires C, 64·7 and H, 6·5%).

(*b*) *From 7-methoxy-5-ethoxy-6-hydroxy-4-methyl coumarin.*—7-Methoxy-5-ethoxy-6-hydroxy-4-methyl coumarin (0·4 g.) was ethylated with diethyl sulphate (0·5 g.) and the product worked up as in the above experiment. It crystallised from methyl alcohol as colourless long flat needles melting at 168–9°. Mixed melting point with the sample described in experiment (*a*) above was undepresesd.

SUMMARY

Earlier investigations have shown that partial methylation of the 7-position of 6: 7-dihydroxy coumarin is definitely possible. Claims were made by Schmid that in 5: 7-dihydroxy-4-methyl coumarin also partial methylation takes place in the 7-position. But no proof was provided. This has now been given by the ethylation of the partial methyl ether and subjecting it to nuclear oxidation and final ethylation. The product is found to be 7-methoxy-5: 6-diethoxy-4-methyl coumarin which has also been made by an independent and unambiguous method for purposes of comparison. The constitution of the partial methyl ether is thus established as 7-methoxy-5-hydroxy-4-methyl coumarin.

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A NEW EFFECT OF HYDROGEN BOND FORMATION

Part V. A Note on the Behaviour of the 8-Hydroxyl Group in Benzopyrone Derivatives

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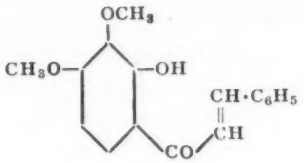
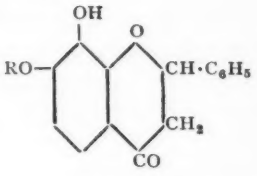
In the isomerisation of flavones, chromones and flavanones[1] having the 5:7:8-arrangement of hydroxyls there was reason to believe that the 8-hydroxyl group played some important part and hence it was considered desirable to get more evidence about the reactivity of this group. It was first recorded by Baker[2] that 7-methoxy-8-hydroxy flavone gave a green colour with ferric chloride. A similar observation was made by Rao and Seshadri[3] in the case of 8-hydroxy-3:5:7:3′:4′-pentamethoxy flavone which was obtained from gossypin. This would indicate the presence of chelation between the 8-hydroxyl and pyrone oxygen. The observation of Shah, Mehta and Wheeler[4] that in the demethylation of wogonin-5-methyl ether using anhydrous aluminium chloride in nitrobenzene solution the 8-methoxyl suffers demethylation along with the 5-methoxyl, provides further support to the existence of this chelation. But efforts to carry out partial methylation of 7:8-dihydroxy flavone have not been successful[2] thus showing that the chelation is only of a weak type.

The position is considerably different in the case of the corresponding flavanones. 2-Hydroxy-3:4-dimethoxy chalkone (I) undergoes demethylation with hydrobromic acid[5] to yield 7-methoxy-8-hydroxy flavanone (II) as a colourless substance quite free from the corresponding chalkone. Further, partial methylation of 7:8-dihydroxy flavanone (II *a*) can also be effected to give rise to a colourless monomethyl ether though slightly impure. It gives a positive ferric reaction and is insoluble in aqueous sodium carbonate and sparingly soluble in sodium hydroxide. This would indicate the existence of a stronger chelation in 8-hydroxy flavanones than in flavones. 7-Methoxy-8-hydroxy flavanone (II) has also been prepared by an alternative procedure starting with the dibenzoate of gallacetophenone-4-methyl ether (III). This is condensed with benzaldehyde in ethyl acetate solution in the presence of dry hydrogen chloride.[6] The dibenzoyloxy chalkone (IV) on hydrolysis with alcoholic potassium hydroxide yields 7-methoxy-8-hydroxy flavanone as the only product. The extraction of most of the product from the alkaline solution by means of ether would indicate the sparing

solubility of the compound in alkali and its formation as the only major product of the reaction shows the existence of chelation (*cf.*, Narasimhachari and Seshadri[7]) rendering the flavanone structure stable.

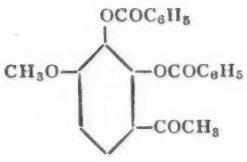


I

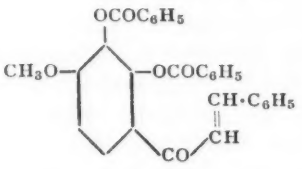


II

II, R = CH_3
II *a*, R = H



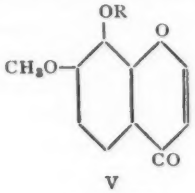
III



IV

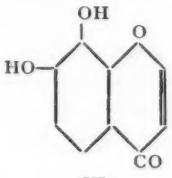
In earlier publications[8] has been explained the similarity between flavanones, chromones and isoflavones in regard to the special properties of the 7-hydroxyl group. In these compounds the 7-hydroxyl undergoes methylation more readily and a methoxyl in this position is far more resistant to demethylation. In earlier work on this feature no compound with a hydroxyl or methoxyl in the 8-position was employed. In view of the interesting results mentioned above using flavanones, similar work has now been carried out with corresponding chromones and isoflavones.

7 : 8-Dimethoxy chromone (V *a*) undergoes easy partial demethylation even with hydriodic acid at 120° giving rise to 7-methoxy-8-hydroxy chromone (V *b*). This substance gives an apple-green colour with ferric chloride and is soluble in sodium carbonate. It is definitely different from 7 : 8-dihydroxy chromone (VI) since it yields a different acetyl derivative and even



V

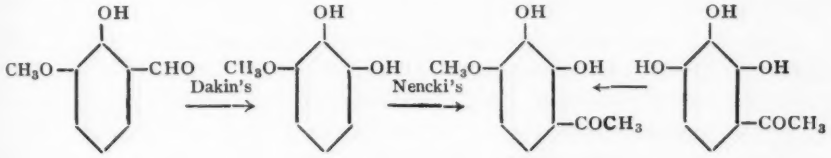
a, R = CH_3
b, R = H



VI

in its ferric chloride colour there is marked difference, the dihydroxy compound giving a deeper green colour. Attempts at partial methylation of 7:8-dihydroxy chromone have not been successful.

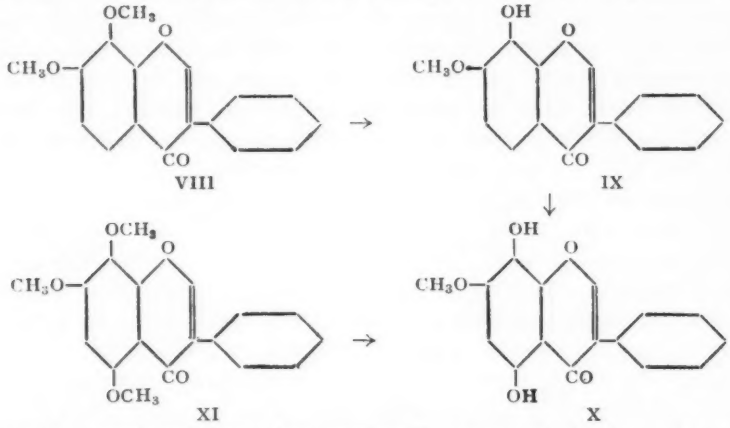
In order to establish the constitution of the above-mentioned demethylation product, 7-methoxy-8-hydroxy chromone (V *b*) has been synthesised by an independent procedure. For this and for the synthesis of 7-methoxy 8-hydroxy flavanone (II) mentioned earlier the 4-methyl ether of gallacetophenone (VII) was needed. There is some confusion in the literature about the monomethyl ether of gallacetophenone. Perkin and Wilson[9] carried out the methylation of monopotassium salt of gallacetophenone and claimed to have obtained in poor yield a monomethyl ether which they described as the 3-methyl ether; it was presumably the 4-methyl ether. They recorded that the product did not give colour with ferric chloride. Baker *et al.*[10] prepared the 4-methyl ether starting from *o*-vanillin, which was converted into monomethyl pyrogallol by Dakin's oxidation and subjected to Nencki's reaction. The preparation of 4-O-methyl gallacetophenone has now been considerably simplified by the direct methylation of gallacetophenone using one mole of dimethyl sulphate in presence of potassium carbonate. The improvement is based on the observation that the hydroxyl *para* to the ketonic group is outstandingly more reactive. This 4-methyl ether of gallacetophenone when condensed with sodium and ethyl formate yields 7-methoxy-8-hydroxy chromone (V *b*) identical with the partial demethylation product of 7:8-dimethoxy compound.



VII

Demethylation of 7:8-dimethoxy isoflavone (VIII) gave results very similar to those of the corresponding chromone. This substance has not been reported before and has now been prepared starting from pyrogallol trimethyl ether which undergoes condensation with phenylacetyl chloride in presence of aluminium chloride to form 2-hydroxy-3:4-dimethoxy phenyl benzyl ketone; final isoflavone condensation[11] with ethyl formate and sodium yields 7:8-dimethoxy isoflavone. This undergoes partial demethylation with hydriodic acid to yield 7-methoxy-8-hydroxy isoflavone (IX). Its constitution has been confirmed by nuclear oxidation with alkaline persulphate whereby 7-methoxy-5:8-dihydroxy isoflavone (X) is obtained in good

yield. This product is found to be identical with the one obtained by the partial demethylation of 5: 7: 8-trimethoxy isoflavone (XI), and represents a successful example of nuclear oxidation from a 8-hydroxy compound to a 5: 8-dihydroxy compound. The reverse oxidation process is more common. Baker[12] reported earlier poor yield in the oxidation of 8-hydroxy-4′-methoxy flavone to the corresponding 5: 8-dihydroxy-4′-methoxy compound.



It may be mentioned here that gossypetin pentamethyl ether with a free 8-hydroxyl group, 7-methoxy-8-hydroxy chromone and isoflavone are easily soluble in aqueous sodium carbonate, whereas the corresponding 7-methoxy-8-hydroxy flavanone is insoluble.

The results recorded in this paper may be summarised as follows. The 8-hydroxyl group in chromone derivatives is involved in chelation as indicated by the positive ferric reaction. But the solubility of the 8-hydroxy compound in aqueous sodium carbonate and the inability of 7 : 8-dihydroxy derivatives to undergo partial methylation in the flavone, isoflavone and chromone series indicates that the chelation is only of a weak type. The chelation is considerably stronger in the flavanones which agrees with the insolubility of 7-methoxy 8-hydroxy flavanone in aqueous sodium carbonate and its very sparing solubility in aqueous sodium hydroxide and also the stability of this flavanone in alkaline medium. The effect of the 8-hydroxyl corresponds to that of the 5-hydroxyl group[7] and 2′-hydroxyl group[13] in this stabilisation.

EXPERIMENTAL

7-Methoxy-8-hydroxy flavanone (II)

(i) *By the demethylation of 2-hydroxy-3: 4-dimethoxy chalkone (I) with hydrobromic acid.*—2-Hydroxy-3: 4-dimethoxy chalkone[15] (1·0 g.) was

dissolved in glacial acetic acid (5 c.c.) and the solution treated with a saturated solution of hydrobromic acid in glacial acetic acid (10 c.c.). After leaving at room temperature for 24 hours it was heated on a boiling water-bath for 30 minutes, cooled and diluted with water (40 c.c.). The brown solid that separated was filtered, washed with water and crystallised first from acetone-petroleum ether mixture and subsequently from alcohol. It separated from alcohol as colourless flat needles and narrow rectangular plates, melting at 153–4°. It gave a green colour with ferric chloride in alcoholic solution. It was insoluble in aqueous sodium carbonate (5%) and sparingly soluble in aqueous sodium hydroxide. Thus it agreed in all its properties with those required for 7-methoxy-8-hydroxy flavanone (II) (Found: C, 71·0; H, 5·2; $C_{16}H_{14}O_4$ requires C, 71·1; H, 5·2%).

(ii) *By synthesis*: *Gallacetophenone-4-methyl ether* (*VII*).—Gallacetophenone (2 g.) was refluxed in acetone solution (30 c.c.) with dimethyl sulphate (1·0 c.c.) and anhydrous potassium carbonate (2·5 g.) for 3 hours. The potassium salts were filtered off and acetone removed from the filtrate. The residue was treated with cold alcohol (10 c.c.) when an almost colourless solid separated. It was filtered and twice crystallised from excess of alcohol from which it was obtained as colourless aggregates of short prisms melting at 127–8°. It dissolved slowly in aqueous sodium carbonate giving a yellow solution and gave a deep greenish brown colour with ferric chloride in alcoholic solution (Found: C, 53·6; H, 6·4; $C_9H_{10}O_4$, H_2O requires C, 54·0; H, 6·0%). Yield 0·9 g. Perkin and Storey[9] reported the melting point of the monomethyl ether they prepared as 134–5° and Baker *et al.*[10] gave the melting point of 132° for the compound obtained by them. While the former reported that their product gave no colour with ferric chloride, Baker *et al.*[10] did not record the ferric reaction of their methyl ether.

The diacetate obtained by the acetic anhydride-pyridine method crystallised from alcohol as colourless thick rectangular plates melting at 150–1° (Found: C, 58·2; H, 4·8; $C_{13}H_{14}O_6$ requires C, 58·7; H, 5·3%). Perkin and Storey[9] reported the same melting point for the diacetate of their product. Deacetylation of the pure acetate gave the dihydroxy compound (melting point and mixed melting point 127–8°).

Dibenzoate (*III*).—The benzoylation of the dihydroxy monomethoxy ketone was carried out using 2 moles of benzoyl chloride and pyridine. The dibenzoate crystallised for alcohol as pale-yellow stout rhombohedral prisms melting at 185–6° (Found: C, 68·7; H, 4·5; $C_{23}H_{18}O_6$, $\frac{1}{2}H_2O$ requires C, 69·2; H, 4·8%).

Condensation with benzaldehyde.—The above dibenzoate of gallacetophenone-4-methyl ether (1·2 g.) was dissolved in dry ethyl acetate (150 c.c.)

and benzaldehyde (0·5 c.c.) added to it. The solution was cooled in ice and a current of dry hydrogen chloride passed through it for 4 hours. It was left in the ice-bath for 24 hours and ethyl acetate removed under reduced pressure on a water-bath. The resulting 2: 3-dibenzoyloxy-4-methoxy chalkone was directly hydrolysed by refluxing with alcoholic potassium hydroxide (0·8 g. in 30 c.c.) for 30 minutes. After removing alcohol under reduced pressure, water was added when a sticky mass separated which was directly taken in ether. The ether solution was marked (A) and the aqueous solution (B). On evaporating the ether solution (A) an almost colourless solid was obtained which crystallised from alcohol as colourless flat needles and narrow rectangular plates melting at 153–4°. It gave a green colour with ferric chloride in alcoholic solution and was insoluble in aqueous sodium carbonate. It was identical with 7-methoxy-8-hydroxy flavanone (II) obtained earlier and a mixed melting point with that sample was undepressed. The aqueous solution (B) on acidification yielded a pale coloured sticky solid which was extracted with ether and the ether solution washed with sodium bicarbonate and water. When the ether extract was evaporated it gave 7-methoxy-8-hydroxy flavanone identical with the above product. Total yield 0·3 g.

7: 8-*Dihydroxy flavanone* (*II a*)

This was claimed to have been prepared earlier by the ring closure of 2: 3: 4-trihydroxy chalkone obtained by direct condensation of gallacetophenone and benzaldehyde.[14] It has now been prepared by the demethylation of 7: 8-dimethoxy flavanone with aluminium chloride in benzene solution.

7: 8-Dimethoxy flavanone[15] (1·0 g.) was refluxed in benzene solution (20 c.c.) with anhydrous aluminium chloride (2·0 g.) for 2 hours. On distilling off benzene and decomposing the aluminium chloride complex a pale yellow solid separated. It was filtered, washed with water and after drying was crystallised from benzene when it was obtained as colourless aggregates of thin rectangular plates melting at 167–8° (Shinoda[14] reported the melting point of 184° for the compound obtained by him). When crystallised from alcohol 7: 8-dihydroxy flavanone separated as colourless long rectangular plates and rods melting at 167–8°. It gave a deep bluish green colour with ferric chloride and was easily soluble in aqueous sodium carbonate (Found in the sample crystallised from alcohol; C, 55·9; H, 5·5; loss on drying 19·0; $C_{15}H_{12}O_4$, 3·5 H_2O requires C, 56·4; H, 5·9; loss on drying, 19·7%. Found in a sample crystallised from benzene: C, 75·3; H, 5·7; $C_{15}H_{12}O_4$, C_6H_6 requires C, 75·5; H, 5·4%).

7: 8-Dimethoxy chromone (V a) and 7: 8-dihydroxy chromone (VI)

Pulverised sodium (1·0 g.) cooled in ice was treated with a solution of gallacetophenone-3: 4-dimethyl ether (2·0 g.) in ethyl formate (15 c.c.). The flask was left corked in the refrigerator for 48 hours. Pieces of crushed ice were then added and since no solid separated the aqueous solution was acidified with ice-cold hydrochloric acid. The colourless solid that separated was filtered and washed with water. It was found to dissolve almost completely in aqueous sodium hydroxide. On extracting the alkaline solution with ether and evaporating the extract a very small quantity (A) (0·1 g.) of a colourless solid was obtained. It crystallised from alcohol as colourless needles, melting at 123–4°. It gave no colour with ferric chloride in alcoholic solution and was insoluble in aqueous sodium hydroxide. Kostanecki[16] reported 124° as the melting point for 7: 8-dimethoxy chromone.

When the alkaline solution left after ether extraction was acidified it gave a colourless product which crystallised from alcohol as hexagonal prisms melting at 156–7° with evolution of gas and solidification and remelting at 202° with decomposition. Yield 1·5 g. It gave a pink colour with ferric chloride in alcoholic solution. It was insoluble in aqueous sodium carbonate but soluble in sodium hydroxide solution. Thus it agreed in all its properties with ω-formyl-gallacetophenone-3: 4-dimethyl ether (Found: C, 59·1; H, 5·7; $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·4%).

Hydriodic acid (10 c.c., sp.gr. 1·7) was added to a cooled solution of ω-formyl-gallacetophenone-3: 4-dimethyl ether (0·5 g.) in acetic anhydride (2 c.c.). The reaction mixture was then heated at 140° for 2 hours and after cooling it was diluted with sulphurous acid. The pale-pink solid that separated was crystallised from alcohol when it was obtained as rectangular prisms and prismatic rods, melting at 262–3° (decomp.). Yield 0·4 g. It gave a bright olive green colour with ferric chloride in alcoholic solution which changed to blue on dilution with water (Kostanecki reported 262° as the melting point for 7: 8-dihydroxy chromone).

On methylating the above 7: 8-dihydroxy chromone (0·4 g.) with excess of dimethyl sulphate (2·2 moles, 0·6 c.c.) and potassium carbonate (1·5 g.) in acetone solution (10 c.c.), 7: 8-dimethoxy chromone was obtained which crystallised from dilute alcohol as colourless needles, melting at 123–4° identical in its properties with the alkali-insoluble portion (A) described above. The mixture of the two samples also melted at 123–4°. Yield 0·35 g.

7-Methoxy-8-hydroxy chromone (V b)

(i) *By partial demethylation with hydriodic acid using the ω-formyl derivative.*—The ω-formyl derivative of gallacetophenone dimethyl ether

(0·4 g.) described in the previous experiment was dissolved in aceti anhydride (2 c.c.) and the solution treated with cooling with hydriodic acid (6 c.c., sp.gr., 1·7). The mixture was heated at 120° in an oil-bath for half an hour, after which it was cooled, diluted with sulphurous acid and the solution extracted with ether. After washing the ether solution with sodium bicarbonate, ether was evaporated and the white crystalline solid left behind was crystallised from alcohol. It separated as colourless small squares and rectangular prisms melting at 202-3°. It gave an apple green colour with ferric chloride and was soluble in aqueous sodium carbonate. It was different from 7: 8-dihydroxy chromone in its reactions and properties and was identical with the product obtained by the other methods described below.

(ii) *By the partial demethylation with hydriodic acid using* 7: 8-*dimethoxy chromone* (*V a*).—7: 8-Dimethoxy chromone (1·0 g.) was heated in acetic anhydride solution (4 c.c.) with hydriodic acid (10 c.c., sp.gr. 1·7) at 120° in an oil-bath for 30 minutes. On working up as in similar cases and crystallising from alcohol, the product was obtained as colourless squares and rectangular prisms melting at 202–3°. It gave an apple green colour with ferric chloride and was easily soluble in sodium carbonate. It was different from 7: 8-dihydroxy chromone (melting point 262°) (Found: C, 62·6; H, 4·6; $C_{10}H_8O_4$ requires C, 62·5; H, 4·2%).

On acetylation the monoacetate was obtained which crystallised from alcohol as colourless elongated rectangular rods and prisms melting at 148–9° (7: 8-diacetoxy chromone has a melting point 110°).

(iii) *By synthesis.*—Pulverised sodium (1·0 g.) cooled in ice was treated with a solution of gallacetophenone-4-methyl ether (VII) (1 g.) in ethyl formate (10 c.c.). The mixture turned gradually orange yellow and deep brown. It was left in the refrigerator for 48 hours after which it was treated with crushed ice and the clear solution acidified with hydrochloric acid. The solution was directly extracted with ether and the ether extract concentrated. On crystallising the solid thus obtained, from excess of alcohol, a small quantity (0·2 g.) separated as the first crop which, when recrystallised from alcohol was obtained as colourless small squares and rectangular prisms melting at 202–3°. It gave an apple green colour with ferric chloride and was identical with 7-methoxy-8-hydroxy chromone described in the earlier two experiments. The alcoholic solution on concentration gave a product (melting point 200–220°) which appeared to be a mixture. It was directly refluxed in alcoholic sulphuric acid (4%) solution for 20 hours. On concentrating the alcoholic solution to half the volume and diluting it with water a colourless solid was obtained, which when crystallised from alcohol,

yielded 7-methoxy-8-hydroxy chromone (melting point and mixed melting point 202–3°). Yield 0·5 g.

If in the above experiment at the end of the condensation, the solution was acidified and allowed to stand for 24 hours at room temperature and then ether extracted, the product was found to be pure 7-methoxy-8-hydroxy chromone (melting point 202–3°). Yield 0·7 g. from 1 g. of the ketone.

2-Hydroxy-3: 4-dimethoxy phenyl benzyl ketone

Anhydrous aluminium chloride (20 g.) was dissolved in ice-cold dry ether (100 c.c.) and pyrogallol trimethyl ether (10 g.) in dry ether (100 c.c.) added to it. The mixture was then treated with phenyl acetyl chloride (9 c.c.) with frequent shaking and the reaction mixture left at room temperature overnight. Ether was then removed on a water-bath, and the aluminium chloride complex decomposed with ice and hydrochloric acid. The hydrolysis was completed by heating it on a water-bath for a few minutes. After cooling the product was taken up in ether, the ethereal solution first washed with sodium carbonate and then extracted four times with aqueous sodium hydroxide (10%) using 25 c.c. for each extraction. The combined alkali extract on acidification deposited a colourless solid which crystallised from alcohol as colourless small rectangular prisms melting at 106–7°. Yield 10 g. It gave a pink colour with ferric chloride (Found: C, 70·5; H, 6·2; $C_{16}H_{16}O_4$ requires C, 70·6: H, 5·9%).

7: 8-Dimethoxy isoflavone (VIII)

A solution of 2-hydroxy-3: 4-dimethoxy phenyl benzyl ketone (2 g.) in ethyl formate (10 c.c.) was added to pulverised sodium (1 g.) cooled in ice and after leaving at 0° for 24 hours the mixture was treated with ice and hydrochloric acid. The colourless solid so obtained was filtered, washed with aqueous sodium hydroxide to remove the unchanged ketone and crystallised from alcohol. 7: 8-Dimethoxy isoflavone separated from alcohol as stout elongated rectangular prisms melting at 133–4°. It gave no colour with ferric chloride (Found: C, 71·8; H, 5·1; $C_{17}H_{14}O_4$ requires C, 72·3; H, 5·0%).

7-Methoxy-8-hydroxy isoflavone (IX)

Hydriodic acid (6 c.c., sp.gr. 1·7) was added slowly to a cooled solution of 7: 8-dimethoxy isoflavone (0·4 g.) in acetic anhydride (2 c.c.) and the solution heated at 120° for 30 minutes.[8] The product that separated on diluting the solution with sulphurous acid was filtered, washed with water and crystallised from alcohol when it separated as colourless stout prisms, melting at 203–5°. Yield 0·3 g. It dissolved in aqueous sodium hydroxide

and sodium carbonate giving a yellow solution, and gave an apple green colour with ferric chloride (Found: C, 71·6; H, 4·8; $C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5%).

7-Methoxy-8-acetoxy isoflavone obtained by acetylation crystallised from ethyl acetate as colourless rectangular prisms and prismatic needles melting at 194–5° (Found: C, 69·7; H, 4·5; $C_{18}H_{14}O_5$ requires C, 69·7; H, 4·5%). Deacetylation of the pure acetate by alcoholic hydrochloric acid yielded the original hydroxy compound (melting point and mixed melting point 203–5°). Both the hydroxy compound and the acetate differed considerably from 7: 8-dihydroxy isoflavone and its acetate described below.

7: 8-*Dihydroxy isoflavone*

(i) *By the demethylation with hydriodic acid.*—Demethylation of 7: 8-dimethoxy isoflavone (0·5 g.) in acetic anhydride solution with hydriodic acid at 140° for 2 hours yielded 7: 8-dihydroxy isoflavone which crystallised from alcohol as colourless flat needles and long rectangular plates melting at 218–20°. It gave an olive green colour with ferric chloride and dissolved readily in aqueous sodium carbonate. Yield 0·3 g. (Found: C, 68·3; H, 4·5; loss on drying 3·6; $C_{15}H_{10}O_4$, $\frac{1}{2}$ H_2O requires C, 68·4; H, 4·2; loss on drying 3·4%).

The diacetate crystallised from ethyl acetate as aggregates of colourless thin plates melting at 139–40° (Found: C, 64·2; H, 4·4; $C_{19}H_{14}O_6$, H_2O requires C, 64·1; H, 4·5%).

(ii) *By the demethylation with aluminium chloride.*—7: 8-Dimethoxy isoflavone (0·2 g.) was refluxed in benzene solution (10 c.c.) with anhydrous aluminium chloride (1 g.) for 2 hours. The dihydroxy isoflavone obtained on removing benzene and decomposing the complex crystallised from alcohol as colourless rectangular plates and needles melting at 218–20° and was identical with the product obtained in the above experiment.

7-*Methoxy*-5: 8-*dihydroxy isoflavone* (*X*)

(i) *By the nuclear oxidation of 7-methoxy-8-hydroxy isoflavone* (*IX*).—A solution of sodium persulphate (1 g. in 10 c.c.) was added dropwise to a stirred solution of 7-methoxy-8-hydroxy isoflavone (0·25 g.) in aqueous sodium hydroxide (15 c.c., I N), the temperature being kept between 15–20°. The stirring was continued for 3 hours and the solution was kept corked for 12 hours. It was then acidified to congo red and the unreacted 7-methoxy-8-hydroxy isoflavone removed by twice extracting with ether. The aqueous solution was then treated with concentrated hydrochloric acid (10 c.c.) after the addition of sodium bisulphite (1 g.) and then heated at 90°

on a water-bath for 20 minutes. A bright yellow compound gradually separated. After cooling it was directly extracted with ether and the ethereal solution dried over anhydrous sodium sulphate. On evaporating the ether solution a bright yellow solid was left behind which crystallised from alcohol as yellow laminæ melting at 208–10° (decomp.). It gave a deep red colour with ferric chloride in alcoholic solution and dissolved readily in aqueous sodium carbonate. It agreed in its properties and reactions with a sample of 7-methoxy-5: 8-dihydroxy isoflavone described below and the mixed melting point was undepressed (Found: C,67·1; H, 4·3; $C_{16}H_{12}O_5$ requires C, 67·6; H, 4·2%). Yield 0·6 g.

(ii) *By partial demethylation of* 5: 7: 8-*trimethoxy isoflavone* (*XI*) *with hydriodic acid.*—An acetic anhydride solution of 5: 7: 8-trimethoxy isoflavone[17] (0·5 g. in 3 c.c.) was heated with hydriodic acid (8 c.c.) at 120° for 30 minutes and the product worked up. The bright yellow 7-methoxy-5: 8-dihydroxy isoflavone thus obtained crystallised from alcohol as yellow laminæ melting at 208–10° (decomp.). It gave a deep red colour with ferric chloride and was easily soluble in aqueous sodium carbonate.

Summary

Past records indicate that an 8-hydroxyl group in a flavone is involved in chelation but it is of a weak nature. 7-Methoxy-8-hydroxy flavanone can be easily obtained by the partial methylation of 7: 8-dihydroxy flavanone or the partial demethylation of 7: 8-dimethoxy flavanone, and can also be directly obtained from gallacetophenone-4-methyl ether. Its preparation and properties indicate the existence of stronger chelation involving the 8-hydroxyl group. Similar experiments have been done on the preparation of 7-methoxy-8-hydroxy chromone and isoflavone. Though the partial demethylation of 7: 8-dimethoxy compounds has been successful, partial methylation of the dihydroxy compounds has not been possible in these cases. The properties of the products also indicate weaker chelation in the chromone and isoflavone just as in the corresponding flavone. In the course of the synthesis of 7-methoxy-8-hydroxy flavanone and chromone independently for purpose of comparison the preparation of the intermediate gallacetophenone 4-methyl ether has been re-investigated and a convenient method has been worked out.

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NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

Part XLIII. The Preparation and *p*-Oxidation of Flavones Analogous to Datiscetin and Morin

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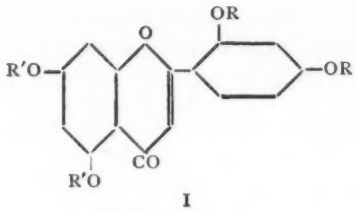
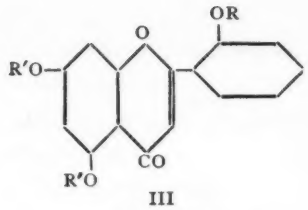
HYDROXY or methoxy flavones with a hydroxyl or methoxyl group in the 2′-position are of rare occurrence. The two definitely known examples belonging to the flavonol series are (i) datiscetin (2′: 3: 5: 7-tetrahydroxy flavone) and (ii) morin (2′: 4′: 3: 5: 7-pentahydroxy flavone). Lotoflavin[1] was considered to be a member of this type belonging to the flavone series (5: 7: 2′: 4′-tetrahydroxy flavone) (I *a*). Synthesis of a substance of this constitution was made by Robinson and Venkataraman[2] using the general procedure of Allan and Robinson; it involved a stage of demethylation with hydriodic acid. The properties of the product were different from those of lotoflavin whose constitution has therefore remained unsettled. At about the same time Algar, Cullinane and Ryan[3] condensed phloracetophenone dimethyl ether with the ester of dimethyl-β-resorcylic acid and subjected the diketone thus obtained to treatment with hydriodic acid. They considered this product to be 5: 7: 2′: 4′-tetrahydroxy flavone (I *a*) and reported that it resembled lotoflavin in its properties. However when phloracetophenone trimethyl ether was employed in this synthesis the isomeric 7: 2′: 4′: 6′-tetrahydroxy flavone (II) was reported to have been obtained. More recently Philbin and Wheeler[4] have in a preliminary note recorded that this type of isomerisation takes place in the presence of hydriodic acid under pressure at elevated temperatures. In order to throw more light on this problem the synthesis of 5: 7: 2′-trihydroxy (III *a*) and 5: 7: 2′: 4′-tetrahydroxy (I *a*) flavones has now been repeated using as demethylating agent, anhydrous aluminium chloride which is known to produce no isomeric change and also hydriodic acid. The products obtained by the two methods are found to be identical showing thereby that under the ordinary conditions of demethylation with hydriodic acid, isomeric change involving 2′-hydroxy group does not occur. This has also been confirmed by remethylating the hydroxy flavone in one case as mentioned below.

The preparation of 5: 7: 2′-trihydroxy flavone (III *a*) was made earlier by Kostanecki and Webel[5] by the condensation of phloracetophenone trimethyl



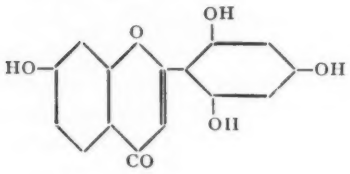
I

a, R = R′ = H
b, R = CH_3, R′ = H
c, R = R′ = CH_3

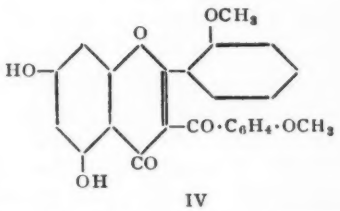


III

a, = R = R′ = H
b, = R = CH_3, R′ = H
c, = R = R′ = CH_3



II



IV

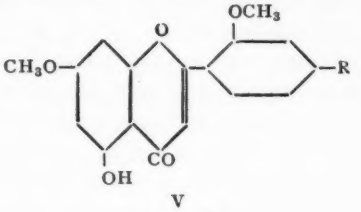
ether with *o*-methoxy benzoic ester and subsequent ring closure and demethylation of the resulting diketone with hydriodic acid. For our present work phloracetophenone has been condensed with the anhydride and sodium salt of O-methyl salicylic acid. The 3-acyl derivative (IV) is obtained as an intermediate stage and is deacylated by boiling with sodium carbonate solution. The resulting 2′-methoxy-5 : 7-dihydroxy flavone (III *b*) is demethylated by boiling with hydriodic acid for 3 hours. The demethylation of this substance could not be effected using anhydrous aluminium chloride because of its sparing solubility in benzene. This difficulty is overcome by fully methylating it to 5 : 7 : 2′-trimethoxy flavone (III *c*) which is soluble in benzene and undergoes demethylation smoothly. The samples of trihydroxy flavone obtained by both the methods are found to be identical and hence it could be concluded that there is no isomeric change during demethylation by boiling with hydriodic acid.

5 : 7-Dihydroxy-2′ : 4′-dimethoxy flavone (I *b*) has been prepared according to the method of Robinson and Venkataraman (*loc. cit.*) using phloracetophenone and the anhydride and sodium salt of 2 : 4-dimethoxy benzoic acid. Better yield of the pure product is obtained by introducing a stage of boiling with sodium carbonate in order to hydrolyse any 3-acyl group. This dimethyl ether is directly demethylated with hydriodic acid and also the tetramethyl ether (I *c*) prepared from it is subjected to demethylation with anhydrous aluminium chloride. Products from the two methods are again found to be identical. It may be concluded that in these cases the pyrone

ring does not undergo opening under the conditions adopted and hence no rearrangement is brought about. That there is no isomeric change during the demethylation with hydriodic acid has been further confirmed by re-methylating the product whereby the original tetramethyl ether (I *c*) is obtained.

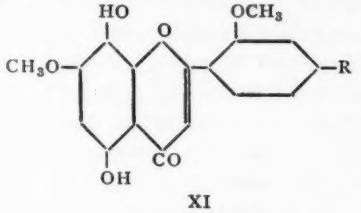
The experiments of Algar, Cullinane and Ryan[3] have now been repeated. From the results reported in the experimental part of this paper, it is clear that the tetrahydroxy flavone sample obtained by them was impure. Purification has now been effected by conversion into the acetate and the subsequent deacetylation. The purified product agrees in every respect with the sample obtained by Robinson and Venkataraman and differs markedly from lotoflavin. Thus all doubts regarding the nature of tetrahydroxy flavone (I *a*) obtained by different methods are cleared up.

In earlier parts of this series a number of typical examples of *p*-nuclear oxidation of flavones have been described. Particular mention may be made of Parts II[6] and XVIII[7] in which nuclear oxidations of chrysin, tectochrysin, acacetin and higher members were reported. The products were the derivatives of 5: 7: 8-hydroxy flavones. Members of this flavone series are not so common, wogonin being the only naturally occurring member. Nobiletin may also be said to belong to this series, but it also contains further a substituent in the 6-position. In earlier work[7] another interesting point was brought out. The 5: 7: 8-hydroxy or methoxy compounds which are easily prepared synthetically undergo isomeric change during demethylation with hydriodic acid to yield members of the 5: 6: 7-hydroxy series which are more commonly occurring. This provides in fact a more handy method of synthesising these compounds. The nuclear oxidation of 5: 7-dihydroxy-2′: 4′-dimethoxy flavone (I *b*) with alkaline persulphate does not proceed satisfactorily. On the other hand, the trimethyl ether (V *a*) with only the 5-hydroxyl free undergoes this oxidation fairly well. The resulting quinol (VI *a*) on methylation yields 5: 7: 8: 2′: 4′-pentamethoxy flavone. Similarly 5-hydroxy-7: 2′-dimethoxy flavone (V *b*) has been obtained by the partial



V

a, R = OCH_3
b, R = H



XI

a, R = OCH_3
b, R = H

methylation of the 2′-methyl ether (III *b*) and this is oxidised with alkaline persulphate. Final methylation of this quinol (VI *b*) gives 5 : 7 : 8 : 2′-tetramethoxy flavone.

EXPERIMENTAL

5 : 7-*Dihydroxy*-2′-*methoxy flavone* (*III b*)

An intimate mixture of phloracetophenone (5 g.), *o*-methoxy benzoic anhydride (35 g.) and sodium *o*-methoxy benzoate (12 g.) was heated under reduced pressure at 180–85° for a period of 5 hours. The semi-solid mass so obtained was suspended in alcohol (150 c.c.) and refluxed with alkali (10 g. potassium hydroxide in 10 c.c. water) for 10 minutes. The alcohol was removed under reduced pressure and the residue dissolved in water (500 c.c.). The solution was filtered and extracted once with ether. It was then saturated with carbon dioxide for 3 hours when the crude 3-acyl derivative (IV) separated out. It was filtered and washed with water. It crystallised from alcohol in the form of almost colourless long thick prisms melting at 244–45° (Found: C, 68·9; H, 4·9; $C_{24}H_{18}O_7$ requires C, 69·0; H, 4·3%). It was hydrolysed by refluxing with aqueous sodium carbonate (5%; 300 c.c.) for 4 hours. The carbonate solution was cooled and acidified with hydrochloric acid. The solid that separated out was filtered and washed with sodium bicarbonate solution to remove the *o*-methoxy benzoic acid formed. The remaining flavone crystallised from alcohol as clusters of small prisms melting at 273–75°. Yield 2·5 g. It dissolved to a yellow solution in sulphuric acid giving pale blue fluorescence. With alcoholic ferric chloride, it gave a reddish brown colour and it dissolved in aqueous sodium hydroxide to give a pale-yellow solution (Found: C, 67·4; H, 4·3; $C_{16}H_{12}O_5$ requires C, 67·4; H, 4·6%).

5-*Hydroxy*-7 : 2′-*dimethoxy flavone* (*V b*)

This compound had earlier been made by Kostanecki and Webel[5] by the action of methyl iodide and potassium hydroxide on an alcoholic solution of 5 : 7 : 2′-trihydroxy flavone (III *a*). For the present work it was prepared by refluxing 5 : 7-dihydroxy-2′-methoxy flavone (III *b*) (1·0 g.) in dry acetone solution (100 c.c.) with redistilled dimethyl sulphate (0·35 c.c., I mole) and ignited potassium carbonate (5 g.) for 8 hours. The acetone solution was filtered and the potassium salts (A) washed with hot acetone. On removal of the solvent from the filtrate, the 5-hydroxy compound admixed with a small quantity of the fully methylated flavone was obtained. The mixture was treated with dilute alkali and the trimethyl ether removed by extraction with ether. The alkaline solution was acidified and the 5-hydroxy compound filtered and washed with water. The residual potassium salts (A) were

stirred up with water and acidified giving a little more of the 5-hydroxy compound. On recrystallisation from alcohol, the dimethyl ether came out as clusters of pale yellow needles and rods melting at 155–56°; yield (0·8 g.). It gave a brown red colour with ferric chloride in alcoholic solution (Found: C, 68·4; H, 4·7; $C_{17}H_{14}O_5$ requires C, 68·5; H, 4·7%).

5:7:2′-*Trimethoxy flavone* (*III c*)

5:7-Dihydroxy-2′-methoxy flavone (0·8 g.) in dry acetone was treated with excess of dimethyl sulphate and anhydrous potassium carbonate and the mixture was refluxed on a water-bath for 30 hours. The acetone solution was filtered and the potassium salts were washed with hot acetone. After distilling off the solvent, ice-water was added and the mixture allowed to stand in the refrigerator overnight. The pale yellow product that separated out was filtered and washed with water. It crystallised from alcohol as colourless needles melting at 176–77°. Yield, 0·6 g. It did not dissolve in sodium hydroxide solution and gave no colour with ferric chloride in alcoholic solution (Found: C, 69·2; H, 5·5; $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·1%).

Demethylation with hydriodic acid: 5:7:2′-*trihydroxy flavone* (*III a*)

5:7-Dihydroxy-2′-methoxy flavone (1·0 g.) was dissolved in acetic anhydride (15 c.c.) and to the solution hydriodic acid (10 c.c.) was added cautiously with cooling in ice water. The mixture was refluxed for 3 hours at 140° on an oil-bath and then diluted with a strong aqueous sodium sulphite solution. The reddish brown powder that had separated in about an hour was filtered, washed with water and dried. It crystallised from alcohol as pale yellow prisms melting at 283–85°. The melting point reported by Kostanecki and Webel was 281°. Yield, 0·3 g.

Demethylation with aluminium chloride: 5:7:2′-*trihydroxy flavone* (*III a*)

A solution of 5:7:2′-trimethoxy flavone (0·47 g.) in dry benzene (40 c.c.) was treated with powdered aluminium chloride (2 g.) and the mixture heated under reflux for 2 hours. The solvent was then distilled off completely and the residual aluminium chloride complex decomposed by cautiously adding pieces of ice and hydrochloric acid (4 c.c.). The resulting yellow powder was filtered and washed with water. It was purified by dissolving in 10% cold sodium carbonate solution (40 c.c.), filtering the solution and acidifying the filtrate with cold dilute hydrochloric acid. The trihydroxy flavone was obtained in an almost pure condition. It crystallised from alcohol as pale yellow prisms melting at 283–85°. Yield, 0·3 g. The compound developed a red colour with ferric chloride in alcoholic solution and dissolved in

dilute sodium hydroxide giving a yellow solution. In sulphuric acid solution it exhibited green fluorescence. The mixed melting point with the hydriodic acid demethylation product was undepressed.

5: 8-*Dihydroxy*-7: 2′-*dimethoxy flavone* (*VI b*)

To a mechanically stirred solution of 5-hydroxy-7: 2′-dimethoxy flavone (1·3 g.) in a mixture of pyridine (20 c.c.) and alkali (3·0 g. sodium hydroxide in 100 c.c. water) was added dropwise a solution of potassium persulphate (3 g.) during a period of 2 hours, the flask being cooled in a bath of cold water. The stirring was continued for 6 hours more and the solution left for 24 hours. It was then acidified to congo-red, the precipitate of the unchanged compound was filtered and the filtrate was extracted with ether. The solution was then made strongly acidic by the addition of concentrated hydrochloric acid and then heated on a boiling water-bath for 20 minutes. After cooling it was repeatedly extracted with ether, the ether solution distilled to remove the solvent and the quinol crystallised from benzene. The 5: 8-dihydroxy compound was obtained as golden yellow broad thin rectangular plates melting at 193–94°. Yield, 0·35 g. With ferric chloride in alcoholic solution, it gave a greenish brown colour which turned brown red with excess of the reagent. The compound gave a brown red solution in aqueous sodium hydroxide which slowly became colourless (Found: C, 64·9; H, 4·4; $C_{17}H_{14}O_6$ requires C, 65·0; H, 4·5%).

5: 7: 8: 2′-*Tetramethoxy flavone*

The above quinol (0·3 g.) was refluxed in dry acetone solution (20 c.c.) after the addition of dimethyl sulphate (0·3 c.c.) and ignited potassium carbonate (3 g.) for 30 hours. The tetramethyl ether crystallised from dilute alcohol in the form of colourless long thick prisms melting at 107–8°. Yield 0·15 g. It dissolved to a golden yellow solution in concentrated sulphuric acid with no fluorescence (Found: C, 66·7; H, 5·3; $C_{19}H_{18}O_6$ requires C, 66·6; H, 5·3%).

5-*Hydroxy*-7: 2′: 4′-*trimethoxy flavone* (*V a*)

The 5: 7-dihydroxy-2′: 4′-dimethoxy flavone (I *b*) was prepared by a modification of the method of Robinson and Venkataraman.[2] The crude product which usually contained some 3-acyl derivative was boiled for 3 hours with 5% aqueous sodium carbonate. The solution was acidified, the precipitated solid filtered and washed with aqueous sodium bicarbonate and finally with water. It crystallised from alcohol in the form of yellow needles melting at 269–70°.

The dihydroxy flavone (1·0 g.) was partially methylated by refluxing in dry acetone solution (50 c.c.) with dimethyl sulphate (0·3 c.c.; 1 mole) in

the presence of anhydrous potassium carbonate (2 g.) for 10 hours. The product on purification and crystallisation from acetone alcohol mixture was obtained as pale-yellow long thick rods melting at 163–4°. Yield, 0·8 g. It gave a brown-red colour with ferric chloride in alcoholic solution; it did not dissolve in 5% sodium hydroxide solution even on boiling, but only turned yellow due to the formation of a sparingly soluble sodium salt. (Found: C, 65·9; H, 5·6; $C_{18}H_{16}O_8$ requires C, 65·9; H, 6·0%).

5: 7: 2′: 4′-*Tetramethoxy flavone* (*I c*).

It was prepared as usual by the complete methylation of 5: 7-dihydroxy-2′: 4′-dimethoxy flavone (I *b*) in dry acetone solution. On crystallisation from alcohol, the tetra methyl ether came out as colourless prisms melting at 184–86°. Its alcoholic solution gave no colour with ferric chloride.

5: 7: 2′: 4′-*Tetrahydroxy flavone* (*I a*)

Method I.—The tetramethoxy flavone (I *c*) (0·3 g.) was demethylated using dry benzene (30 c.c.) and anhydrous aluminium chloride (2·0 g.) and the product was worked up exactly as in the similar case described earlier. The tetrahydroxy flavone crystallised from alcohol in the form of woolly needles. On heating in a capillary tube it darkened progressively from 290° onwards and melted down at 332–35°. It was further purified by conversion into the tetra acetate using acetic anhydride and pyridine. The acetate crystallised from benzene as colourless stout prisms melting at 158–59° (Robinson and Venkataraman gave the same melting point). It was deacetylated by boiling with alcoholic hydrochloric acid for half an hour. The product now melted definitely between 332–35° without any previous change.

Method II.—5: 7-Dihydroxy-2′: 4′-dimethoxy flavone (I *b*) was demethylated by boiling with hydriodic acid for two hours and the product worked up in the usual way. After one crystallisation from alcohol, this also darkened progressively from 290° onwards and melted down at 332–35°. Its purity could also be improved by the acetate method. The final sample agreed with the one obtained by method I and the mixed melting point was undepressed. This sample of tetrahydroxy flavone (0·1 g.) was remethylated in anhydrous acetone solution by boiling with excess of dimethyl sulphate and potassium carbonate for 30 hours. The fully methylated product crystallised from dilute alcohol melting at 184–86°. Yield, 70 mg. The mixed melting point with the sample of tetramethoxy flavone (I *c*) described earlier was undepressed.

Method III.—2-Hydroxy-4: 6: 2′: 4′-tetramethoxy benzoylacetophenone was prepared according to the method of Algar, Cullinane and Ryan.[3] It melted at 151°. The diketone (1 g.) was refluxed with acetic anhydride (10 c.c.) and hydriodic acid (10 c.c., d. 1·7) for two hours and the product worked up as in other demethylations. It crystallised from alcohol melting indefinitely between 280–300°. The m.p. did not improve appreciably on repeated crystallisations. It was therefore acetylated using acetic anhydride and pyridine. The acetate crystallised from alcohol melting at 158–59°. The mixed melting point of this acetate with a sample of 5: 7: 2′: 4′-tetraacetoxy flavone obtained by method I was undepressed. The acetate was deacetylated by boiling with alcohol hydrochloric acid mixture (1: 1) and the resulting tetrahydroxy flavone crystallised from alcohol. The purified sample then melted at 332–35°. The mixed melting point with 5: 7: 2′: 4′-tetrahydroxy flavone was undepressed. It dissolved to a pale yellow solution in concentrated sulphuric acid and gave a violet-blue fluorescence.

5: 8-*Dihydroxy*-7: 2′: 4′-*trimethoxy flavone* (*VI a*)

The 5-hydroxy-7: 2′: 4′-trimethoxy flavone (1·3 g.) was dissolved in a mixture of pyridine (20 c.c.) and alkali (3·5 g. sodium hydroxide in 100 c.c. of water) and was subjected to oxidation with potassium persulphate (3·1 g. in 100 c.c.), the flask being cooled in a bath of cold water. The product was worked up as described in the previous case. The recovered original compound amounted to 0·7 g. The oxidation product crystallised from benzene as bright yellow rectangular plates melting at 203–4°. With ferric chloride in alcoholic solution, it gave a greenish brown colour changing to deep brown red with excess. In aqueous sodium hydroxide an orange-red solution was obtained and the colour faded off slowly (Found: C, 62·6; H, 4·6; $C_{18}H_{16}O_7$ requires C, 62·9; H, 5·0%).

5: 7: 8: 2′: 4′-*Penta-methoxy flavone*

The above quinol (0·15 g.) was refluxed for 30 hours in dry acetone solution (20 c.c.) with dimethyl sulphate (0·2 c.c.) and anhydrous potassium carbonate (3 g.). The product crystallised from dilute alcohol as colourless long thin needles, melting at 152–53°. Yield, 0·1 g. (Found: C, 64·5; H, 5·8; $C_{20}H_{20}O_7$ requires C, 64·5; H, 5·3%).

SUMMARY

The synthesis of 5: 7: 2′-trihydroxy and 5: 7: 2′: 4′-tetrahydroxy flavones has been repeated using Allan-Robinson condensation and both hydriodic acid and anhydrous aluminium chloride as demethylating agents. With these

reagents and under ordinary conditions isomeric change involving the 2'-hydroxyl group does not occur. The tetrahydroxy flavone has also now been prepared by the procedure of Algar *et al.* The sample is found to be identical with the one obtained by the method of Robinson and Venkataraman and is different from lotoflavin. The nuclear oxidation of the partial methyl ethers of the two flavones has been carried out using alkaline persulphate.

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A NEW EFFECT OF HYDROGEN BOND FORMATION (CHELATION)

Part VI. Synthesis of 5-Hydroxy-2′-methoxy flavanone and 5: 7-Dihydroxy-2′-methoxy flavanone

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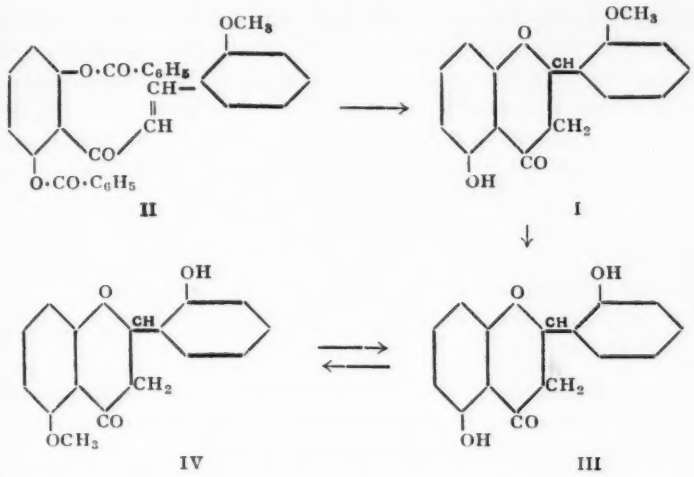
In our earlier paper[1] in this series we recorded the extraordinary properties of 2′-hydroxy flavanones. Attempts to get a 2′-methoxy flavanone by initial chalkone condensation and subsequent ring closure failed in all the cases studied. The remarkable resistance to methylation of the 2′-hydroxyl group makes it impossible to prepare a 2′-methoxy flavanone by methylation. As citronetin[2] is claimed to be 5: 7-dihydroxy-2′-methoxy flavanone attempts have been made to work out methods for the preparation of 2′-methoxy flavanones having free hydroxyl groups in the 5 and 7-positions.

As the simplest example 5-hydroxy-2′-methoxy flavanone (I) has been chosen and it has been prepared by the following procedure. The dibenzoate of γ-resacetophenone is condensed with *o*-methoxy benzaldehyde in dry ethyl acetate solution in presence of dry hydrogen chloride.[3] The resulting dibenzoyloxy-2′-methoxy chalkone (II) is hydrolysed with alcoholic potassium hydroxide. After removal of the alcohol and dilution with water a colourless product separates from the alkaline solution. The analytical values agree with the formula $C_{16}H_{14}O_4$ and its reaction and properties agree with the requirements of the structure of 5-hydroxy-2′-methoxy flavanone. On demethylation with aluminium chloride in dry benzene solution it gives 5: 2′-dihydroxy flavanone (III) which is identical with the compound of the same structure obtained earlier from the similar demethylation of 5-methoxy-2′-hydroxy flavanone (IV) and it forms the same 5-monomethyl ether with excess of dimethyl sulphate. This conversion of 5-hydroxy-2′-methoxy flavanone (I) into the 5-methoxy-2′-hydroxy flavanone (IV) through the intermediate 5: 2′-dihydroxy compound (III) provides further confirmation of the flavanone structure assigned earlier[1] to the products obtained by the direct condensation of 2-hydroxy ketone derivatives with salicylaldehyde.

It was reported earlier that for the preparation of 2-hydroxy-6: 2′-dimethoxy chalkone, the most convenient method was the use of sodium

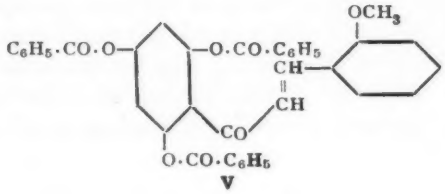


ethoxide as the condensing agent. The same chalkone has now been prepared by the acid condensation using the benzoate of γ-resacetophenone monomethyl ether and *o*-methoxy benzaldehyde followed by the alkaline hydrolysis of the 2-benzoyloxy chalkone. The conditions used for this condensation do not cause a demethylation of the 2′-methoxyl group of the chalkone.

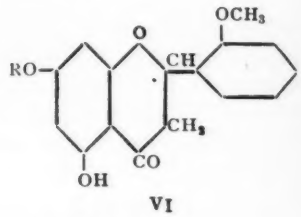
In a previous communication[1] we pointed out the marked differences in regard to the properties of citronetin isolated from Citrus limon ponderosa[2] and the synthetic 5:7-dihydroxy-2′-methoxy flavanone. Shinoda and Sato[4] synthesised the dihydroxy methoxy flavanone by condensing phloroglucinol with *o*-methoxy cinnamoyl chloride in the presence of anhydrous aluminium chloride. In our experience the use of hydroxy compounds in Friedel and Crafts synthesis leads to the formation of resinous by-products and it is difficult to obtain the pure compound. We have therefore examined alternative methods for the synthesis of this flavanone. The acid condensation procedure using the benzoate of the ketone given earlier in this paper gives successful results. Phloracetophenone is converted to the tribenzoate and is then condensed with *o*-methoxy benzaldehyde in dry ethyl acetate solution in the presence of dry hydrogen chloride gas.[3] The tribenzoyloxy chalkone (V) on hydrolysis with alcoholic potassium hydroxide gives 5:7-dihydroxy-2′-methoxy flavanone (VI *a*). The yield of the flavanone is considerably lower than in the case of 5-hydroxy-2′-methoxy flavanone. The melting point of this compound agrees with that recorded by Shinoda and Sato[4] and differs from that of citronetin.[2] The acetate has

now been prepared using acetic anhydride and pyridine and it has a melting point 104–5°; its composition agrees with that of a triacetate. Shinoda and Sato give the melting point of the diacetate as 119°. On partial methylation with one mole of dimethyl sulphate 7: 2′-dimethoxy-5-hydroxy flavanone (VI *b*) is obtained and it agrees with the sample of Shinoda and Sato.[4] This methyl ether undergoes demethylation with anhydrous aluminium chloride in benzene solution and gives 5: 7: 2′-trihydroxy flavanone (VII) which when crystallised from alcohol melts at 195–6° agreeing with the sample described by us earlier[1] and a mixture of the two samples melted at 195–6°. However on recrystallisation from benzene the melting point rises up to 217–18°. In a repetition of the demethylation of 5: 7-dimethoxy-2′-hydroxy flavanone[1] the same results are observed.

The above trihydroxy flavanone was prepared by Shinoda and Sato[4] by the direct condensation of phloroglucinol with 2-carbethoxy cinnamoyl chloride and they reported a melting point of 185–7°.

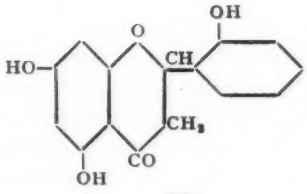


V

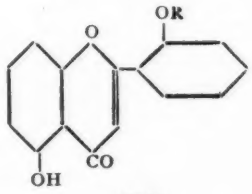


VI

a, R = H
b, R = CH_3



VII



VIII

a, R = CH_3
b, R = H

In the course of attempts to convert 2′-methoxy flavanone derivatives into the corresponding flavones authentic samples of 2′-methoxy flavones were required for purposes of comparison. Further in view of the unusual resistance of the 2′-hydroxyl group of flavanones to methylation a study of the behaviour of the 2′-hydroxyl group in the corresponding flavones was also necessary. Hence 5-hydroxy-2′-methoxy flavone (VIII *a*) has now been

prepared by the Allan Robinson condensation using γ-resacetophenone, the anhydride and sodium salt of *o*-methoxy benzoic acid. This could be demethylated by means of hydriodic acid to yield 5:2′-dihydroxy flavone (VIII *b*).

No rearrangement of the flavone ring is noticed under the usual experimental conditions. This is shown by the formation of the same dihydroxy compound when aluminium chloride which is known to cause no isomeric change in many similar cases studied earlier,[5] is employed for the demethylation (see also Gupta and Seshadri[5]). The experimental conditions under which ring isomeric change was noticed by Philbin and Wheeler[6] in the case of 2′-methoxy flavones are however somewhat special. Partial methylation of 5:2′-dihydroxy flavone yielded the original 5-hydroxy-2′-methoxy flavone. This not only shows that in flavones the 2′-hydroxyl group is fairly readily methylated and that the 5-hydroxyl is as usual more resistant but also emphasises again the remarkable difference between flavanones and flavones in regard to the 2′-hydroxyl group (see also Jain *et al.*[7]). Further the above experimental result confirms the observation that there is no isomeric change during the demethylation of 5-hydroxy-2′-methoxy flavone with hydriodic acid under the usual conditions. Experiments for the oxidation of 2′-hydroxy flavanone derivatives using iodine and sodium acetate[8] have not been successful as the reaction is complicated by the occurrence of iodination. Similar difficulties are encountered in the case of the corresponding 2′-methoxy flavanones, also.

Experimental

5-Hydroxy-2′-methoxy flavanone (I)

γ-Resacetophenone on benzoylation using benzoyl chloride (2 moles) and pyridine yielded the dibenzoate (m.p. 108–10°). The dibenzoate (5 g.) and *o*-methoxy benzaldehyde (2 g.) were dissolved in dry ethyl acetate (70 c.c.) and a current of dry hydrogen chloride passed for 3 hours. The solution became yellow, orange, orange red and finally red. It was kept in an ice-bath overnight free from moisture. Ethyl acetate was then removed under reduced pressure and the dark semi-solid mass was taken in hot alcohol (40 c.c.). The alcoholic solution was refluxed with potassium hydroxide (2 g. in 2 c.c. of water) for 30 minutes after which alcohol was removed completely under reduced pressure. On adding water a pale yellow solid separated out which was filtered, washed with water and crystallised from alcohol. It separated from alcohol in which it was sparingly soluble as colourless rectangular tablets melting at 131–2°. Acidification of the alkaline solution gave some more of the same product. Total yield 1·0 g. 5-Hydroxy-2′-methoxy flavanone gave a reddish violet colour with ferric chloride and a

bright red colour with magnesium and hydrochloric acid in alcoholic solution (Found: C, 71·3; H, 5·6; $C_{16}H_{14}O_4$ requires C, 71·1; H, 5·2%).

5: 2′-*Dihydroxy flavanone* (*III*)

A benzene solution of 5-hydroxy-2′-methoxy flavanone (1 g. in 20 c.c.) was heated for 2 hours with freshly powdered anhydrous aluminium chloride (4 g.). Benzene was then completely removed by distillation and the complex decomposed with ice and hydrochloric acid. The colourless solid thus obtained was filtered, washed with water and after drying crystallised from a mixture of ethyl acetate and petrol from which it separated as colourless rectangular tablets melting at 154–5°. It gave a deep reddish violet colour with ferric chloride. It was identical in its reactions with 5: 2′-dihydroxy flavanone obtained by the similar demethylation of 5-methoxy-2′-hydroxy flavanone[1] and a mixed melting point of the two samples was undepressed.

5-*Methoxy*-2′-*hydroxy flavanone* (*IV*)

The dihydroxy flavanone (0·4 g.) obtained above was methylated by refluxing in acetone solution for 16 hours with excess of dimethyl sulphate (0·4 c.c.) and anhydrous potassium carbonate (1 g.). On working up the methylated product it separated as a sticky mass. It was directly taken up in ether, the ether solution dried over anhydrous sodium sulphate and finally the ether removed by distillation. The residue was then sublimed in vacuum in a hot water-bath when it was obtained as colourless long needles. It gave a green colour with concentrated nitric acid, a reddish violet colour with ferric chloride and melted at 55–6°. Thus it agreed in all its properties with 5-methoxy-2′-hydroxy flavanone and a mixed melting point with the sample described earlier[1] was undepressed.

2-*Hydroxy*-6: 2′-*dimethoxy chalkone*

2-Benzoyloxy-6-methoxy acetophenone was prepared by the benzoylation of 2-hydroxy-6-methoxy acetophenone with benzoyl chloride and pyridine. Rajagopalan *et al.*[9] originally obtained it as a viscous oil. In the present work it was washed with petroleum ether when it solidified. It then crystallised from alcohol as colourless stout prisms melting at 63–4° (Found: C, 69·0; H, 5·2; $C_{16}H_{14}O_4$, $\frac{1}{2}H_2O$ requires C, 68·8; H, 5·4%). The above benzoate (2·7 g.) was condensed with benzaldehyde (1·4 g., 1 mole) in dry ethyl acetate solution at 0° by passing a current of dry hydrogen chloride gas for 4 hours and leaving the mixture at 0° for 24 hours. The product (monobenzoyloxy chalkone) was worked up as in a similar experiment described earlier. The alkaline solution on acidification gave a bright yellow solid. It was filtered, washed with aqueous sodium bicarbonate and

water. On crystallising from alcohol the product separated as bright yellow stout rhombic prisms melting at 96–7°. Yield 0·8 g. It gave a reddish brown colour with ferric chloride, no colour with magnesium and hydrochloric acid and only a red colour with nitric acid. It agreed in its reactions with 2-hydroxy-6: 2′-dimethoxy chalkone[1] and the mixed melting point with that compound was undepressed.

Phloracetophenone tribenzoate

This was originally made by Canter *et al.*[10] The following slightly modified procedure has now been employed. Phloracetophenone (5 g.) was dissolved in pyridine (9 c.c.), the cooled solution treated with benzoyl chloride (10 c.c.) and the mixture kept aside for 2 hours. Pieces of ice were added and the semi-solid mass that was obtained was directly taken up in ether. The ether solution was successively washed with ice-cold dilute hydrochloric acid, aqueous alkali (5%) and finally with water. It was then dried over anhydrous sodium sulphate. On distilling off ether the tribenzoate was obtained as a semi-solid mass which gave no colour with ferric chloride in alcoholic solution. It was directly used for the chalkone condensation since it was pure enough and there was considerable loss on crystallisation.

5: 7-*Dihydroxy-2′-methoxy flavanone* (*VI a*)

The tribenzoate (5 g.) and *o*-methoxy benzaldehyde (1·5 g. 1 mole) were dissolved in dry ethyl acetate and a current of dry hydrogen chloride passed at 0° for 4 hours. On working up the product as already described earlier in a similar case using alcoholic potassium hydroxide (2 g. in 40 c.c.) and acidifying the alkaline solution a coloured product was obtained. It was filtered, washed with aqueous sodium bicarbonate and water and dried. The dry solid repeatedly extracted with a mixture of benzene and petroleum ether (1: 2 in 100 c.c. lots) by refluxing on a hot water-bath. By extracting five or six times the pure colourless product could be completely extracted leaving behind a coloured resinous by-product. The combined benzene-petroleum ether solution was distilled to remove the solvent and it yielded an almost colourless residue. By crystallising twice from methanol 5: 7-dihydroxy-2′-methoxy flavanone was obtained as colourless stellar aggregates of prisms melting at 220–2°. Further crystallisation did not improve the melting point. It gave a pink colour with magnesium and hydrochloric acid and a reddish violet colour with ferric chloride. It readily dissolved in aqueous sodium carbonate (Found: C, 66·9; H, 5·2; $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9%).

Triacetate

The above flavanone (0·1 g.) was refluxed with acetic anhydride (2 c.c.) and 3 drops of pyridine at 140° for 2 hours. On pouring the solution into

ice water (20 c.c.) a colourless solid separated. It was filtered, washed with water and crystallised from absolute alcohol when it came out as colourless small prismatic needles melting at 104–5° (Found: C, 64·1; H, 5·2; $C_{22}H_{20}O_8$ requires C, 64·1; H, 4·9%).

5-Hydroxy-7: 2′-dimethoxy flavanone (VI b)

(i) 5: 7-Dihydroxy-2′-methoxy flavanone (0·3 g.) was boiled for 4 hours with 1 mole of dimethyl sulphate (0·1 c.c.) in acetone solution (20 c.c.) in presence of anhydrous potassium carbonate. The monomethyl ether crystallised from alcohol-benzene mixture as colourless long rectangular tablets melting at 91–2°. It gave a blue colour with concentrated nitric acid and wine red colour with ferric chloride. It was insoluble in aqueous sodium carbonate and sparingly soluble in aqueous alkali. With magnesium and hydrochloric acid it developed a pink colour. It agreed in its properties with 7: 2′-dimethoxy-5-hydroxy flavanone described by Shinoda and Sato[4] who gave the melting point as 91–2° (Found: 68·0; H, 5·4; $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3%).

(ii) On methylating the dihydroxy flavanone (0·2 g.) using methyl iodide (0·5 c.c.) and potassium carbonate in acetone the same partial methyl ether was obtained (m.p. and mixed m.p. 91–92°).

5: 7: 2′-Trihydroxy flavanone (VII)

5-Hydroxy-7: 2′-dimethoxy flavanone (0·2 g.) was refluxed in benzene solution (10 c.c.) with anhydrous aluminium chloride (0·5 g.) for 2 hours. Benzene was then distilled off and the complex decomposed with ice and concentrated hydrochloric acid (4 c.c.). On leaving overnight a colourless crystalline solid separated which was filtered, washed with water. It crystallised from alcohol as colourless thin plates melting at 195–6.° A mixed melting point with our earlier sample of 5: 7: 2′-trihydroxy flavanone was undepressed. This product on recrystallising from dry benzene separated as colourless thin plates melting at 217–18°. Further crystallisation did not raise the melting point. In a repetition of the demethylation of 5: 7-dimethoxy-2′-hydroxy flavanone[1] with aluminium chloride in benzene solution it was found that the product when once crystallised from alcohol melted at 195–6°, but a recrystallisation from benzene raised the melting point to 217–18°. A mixture of the two samples also melted at 216–18°.

5-Hydroxy-2′-methoxy flavone (VIII a)

An intimate mixture of γ-resacetophenone (3 g.), *o*-methoxy benzoic anhydride (20 g.) and sodium salt of *o*-methoxy benzoic acid (4 g.) was heated under reduced pressure at 175–85° for 5 hours. At the end of the reaction

the solid crust was broken up and refluxed with alcohol (40 c.c.) for 10 minutes. It was then treated with alcoholic potash (5·5 g. in 30 c.c.) and refluxed for 15 minutes more. As much alcohol as possible was removed under reduced pressure and excess of water (150 c.c.) added to the residue. A stream of carbon dioxide was passed when a brownish yellow mass separated. The precipitate was filtered and a portion crystallised from alcohol. The 3-acyl derivative of the flavone melted at 180–2°. The bulk of the precipitate was deacylated by refluxing with sodium carbonate solution (5%) for 2 hours. It was then filtered and washed with water. The alkaline filtrate was acidified and the acid recrystallised from dilute alcohol. It then melted at 100° and was identical with *o*-methoxy benzoic acid thus clearly indicating that the 3-acyl derivative was obtained in the condensation. The crude flavone on crystallisation from ethyl acetate gave pale yellow rhombohedral and rhombic prisms melting at 190–1°. It have a deep red colour with ferric chloride and was sparingly soluble in aqueous alkali. Yield 2·5 g. (Found: C, 71·9; H, 4·2; $C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5%).

The above flavone (0·2 g.) was refluxed with acetic anhydride (3 c.c.) and a few drops of dry pyridine for 2 hours at 140°. The product was poured into ice-water (50 c.c.) when a colourless solid separated out. On recrystallisation from absolute alcohol the acetate was obtained as stout rectangular prisms melting at 180–1° (Found: C, 69·2; H, 4·0; $C_{18}H_{14}O_5$ requires C, 69·7; H, 4·5%).

5: 2′-*Dimethoxy flavone*

5-Hydroxy-2′-methoxy flavone (0·2 g.), dimethyl sulphate (0·15 c.c.) and potassium carbonate (1 g.) were refluxed in dry acetone (50 c.c.) for 20 hours. On crystallisation from ethyl acetate, 5: 2′-dimethoxy flavone was obtained in the form of stout prisms melting at 134–5° (Found: C, 71·9; H, 4·7; $C_{17}H_{14}O_4$ requires C, 72·4; H, 5·0%).

5: 2′-*Dihydroxy flavone* (*VIII b*)

(i) *Demethylation with hydriodic acid.*—5-Hydroxy-2′-methoxy flavone (0·4 g.) was dissolved in acetic anhydride (3 c.c.), hydriodic acid (10 c.c.) added and the solution refluxed at 140° for 1 hour. The mixture was cooled and poured into sulphur dioxide water when a pale yellow solid separated which was collected and washed with water. It crystallised from ethyl alcohol as pale yellow prisms melting at 175–6°. It gave a deep red colour with ferric chloride and was sparingly soluble in aqueous sodium hydroxide (Found: C, 70·8; H, 4·0; $C_{15}H_{10}O_4$ requires C, 70·9; H, 3·9%).

(ii) *Demethylation with aluminium chloride.*—5-Hydroxy-2′-methoxy flavone (0·5 g.) was dissolved in dry benzene (20 c.c.) and the solution refluxed with

anhydrous aluminium chloride (2 g.). On working up the product as in similar cases 5: 2′-dihydroxy flavone was obtained as a pale yellow solid. It crystallised from alcohol as pale yellow prisms and was identical with the dihydroxy flavone described in the above experiment (m.p. and mixed m.p. 175–6°).

Partial methylation.—The above dihydroxy flavone (0·5 g.) was refluxed in acetone solution (100 c.c.) with dimethyl sulphate (0·2 c.c. 1 mole) and anhydrous potassium carbonate (1 g.) for 12 hours. The mixture was then filtered and the potassium salts washed with hot acetone. On removing acetone from the filtrate a solid was obtained which crystallised from alcohol as pale yellow rhombohedral and rhombic prisms melting at 190–1° and was identical with 5-hydroxy-2′-methoxy flavone described earlier (mixed m.p. 190–1°). On acetylation it gave an acetate which was identical with 5-acetoxy-2′-methoxy flavone (m.p. and mixed m.p. 180–1°).

SUMMARY

For the preparation of flavanones having a 2′-methoxy group the acid method of chalkone condensation employing benzoates of hydroxy ketones is convenient. 5-Hydroxy-2′-methoxy flavanone and 5: 7-dihydroxy-2′-methoxy flavanone have thus been prepared. By demethylating the former with aluminium chloride 5: 2′-dihydroxy flavanone is obtained which undergoes only partial methylation in the 5-position even with excess of the reagent confirming that the 2′-hydroxyl is highly resistant. Synthetic 5: 7-hydroxy-2′-methoxy flavanone and its derivatives made by us and by Shinoda and Sato agree, but they do not agree in their properties with natural citronetin and its derivatives.

5-Hydroxy-2′-methoxy flavone does not undergo isomeric change under ordinary conditions of demethylation. 5: 2′-dihydroxy flavone undergoes partial methylation smoothly in the 2′-position thus showing the existence of marked difference between flavanones and flavones.

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SYNTHETICAL EXPERIMENTS IN THE CHROMONE GROUP

Part XXVII. Coupling of 5-Hydroxyflavone, 5-Hydroxy-6-methoxyflavone and Tectochrysin with Diazotized Aniline. New Synthesis of 5: 6-Dihydroxyflavone, Baicalein, and 5: 6: 8-Trihydroxyflavone

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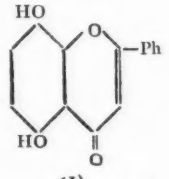
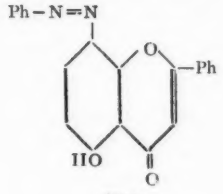
Received December 22, 1952

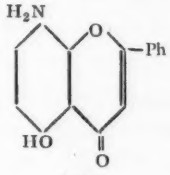
The coupling of 6-hydroxyflavone with diazotized aniline in the 5-position has been used for the synthesis of 5: 6-dihydroxyflavone,[1] and the behaviour of 5-hydroxyflavone and its derivatives towards diazotized aniline has now been studied. 5-Hydroxyflavone in pyridine-alcohol containing caustic soda and ammonia coupled with diazotized aniline. The azo dye, presumably (II), gave on reduction a primary amine which should then be 8-amino-5-hydroxyflavone (III). The diazonium salt from (III) was unusually stable, but on slow boiling with 50% sulphuric acid until the concentration was about 80% decomposition with evolution of nitrogen took place. The product was 5: 6-dihydroxyflavone and not primetin (I). The constitution of the azo dye from 5-hydroxyflavone was therefore examined. When



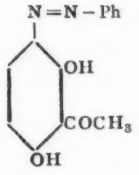
(I)



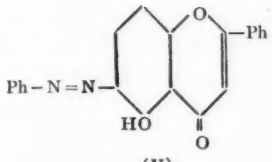
(II)



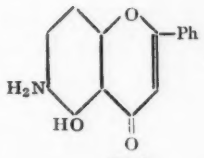
(III)



(IV)



(V)



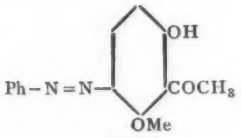
(VI)

2-acetyl-4-benzeneazoresorcinol (IV) was heated with benzoic anhydride and sodium benzoate, the product was a benzeneazo-5-hydroxyflavone

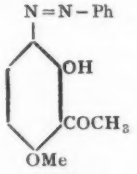
different from (II) and formulated as (V). Cyclization of (IV) in this direction to form (V), and not (II), is to be expected on account of chelation of the azo and *o*-hydroxyl groups. The constitution of (II) and (V) as the 8- and 6-benzeneazo derivatives of 5-hydroxyflavone was confirmed by the fact that (II) could be methylated by means of dimethyl sulphate and potassium carbonate in acetone solution, while (V) was resistant to methylation. Reduction of (V) and diazotization of the aminophenol (VI) thus obtained gave a diazo-oxide in the same manner as 5-amino-6-hydroxyflavone.[1] The amine agreed in its properties with 6-amino-5-hydroxyflavone prepared from 6-acetyl-5-hydroxyflavone by Sugasawa[2] except for a slight difference in the melting point. The melting point observed was 181° (Sugasawa, 177°). Vigorous hydrolysis of the diazo-oxide with sulphuric acid gave 5 : 6-dihydroxyflavone. Sugasawa[2] has stated that all his attempts to replace the amino by hydroxyl in 6-amino-5-hydroxyflavone were unsuccessful.

Since the aminophenols (III) and (VI) were isomeric and not identical compounds, the former was 8-amino-5-hydroxyflavone, and the formation of 5 : 6-dihydroxyflavone, and not 5 : 8-dihydroxyflavone, from (II) and (V) has to be explained by postulating the opening of the pyrone ring under the drastic conditions of acid treatment of the diazonium salt, followed by cyclization in the alternative direction. Such rearrangements have been recorded by Wesseley,[3] Baker[4] and Seshadri[5] during demethylation of flavones containing methoxyl groups in the 5 : 8-positions with hydriodic acid. It was observed in the present work that by boiling with 32% hydrochloric acid or 50–80% sulphuric acid, 8-amino-5-hydroxyflavone (III) was converted into the 6-amino compound (VI), and primetin into 5 : 6-dihydroxyflavone.

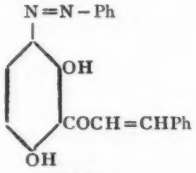
When 2-hydroxy-6-methoxyacetophenone[4] was coupled with benzene diazonium chloride, the dye obtained had the anticipated structure (VII), and was different from the product (VIII) of the methylation of 2-acetyl-4-benzeneazoresorcinol (IV) with one mole of dimethyl sulphate in acetone solution in the presence of potassium carbonate. When (VII) was submitted to the Robinson reaction with benzoic anhydride the result was unexpected. Instead of 6-benzeneazo-5-hydroxyflavone (V) or its methyl ether, 8-benzene-



(VII)



(VIII)

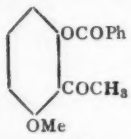


(IX)

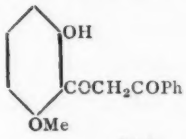
azo-5-hydroxyflavone (II) was obtained. Demethylation occurred, apparently by a direct attack of the anhydride on the methoxyl group, immediate cyclization to (II) then taking place. Demethylation during the Robinson reaction was noticed by Baker[6] in the case of 2: 5-dihydroxy-6-methoxyacetophenone, but the cyclization of the flavone proceeded in the direction to be anticipated and the product was 5: 6-dihydroxyflavone.

The condensation of 2-acetyl-4-benzeneazoresorcinol with benzaldehyde gave the chalkone (IX), which did not undergo cyclization to a flavone by the action of selenium dioxide in amyl alcohol or xylene.

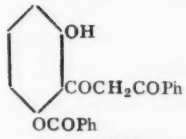
5-Methoxyflavone was first prepared by Simonis and Danishevski,[7] and 5-hydroxyflavone by Sugasawa.[8, 9] Seshadri and co-workers[10] synthesized 5-hydroxyflavone by converting 2-benzoyloxy-6-methoxyacetophenone (X) to the diketone (XI) by means of sodamide in toluene at 100°, cyclization of the diketone to 5-methoxyflavone and demethylation. They also



(X)



(XI)

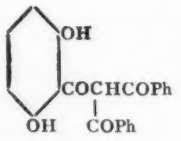


(XII)

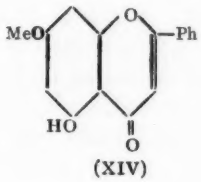
obtained it by debenzoylation of 3-benzoyl-5-hydroxyflavone[9] with alcoholic sodium carbonate. 2-Acetylresorcinol dibenzoate, when treated with sodium ethoxide in absolute alcohol,[11] gave 6-benzoyloxy-2-hydroxydibenzoylmethane (XII), which was converted into 5-hydroxyflavone by the action of glacial acetic acid and fused sodium acetate.

2-Acetylresorcinol dibenzoate, dissolved in ether or boiling benzene and treated with sodamide, gave a compound which is formulated as the triketone (XIII) since it gave 3-benzoyl-5-hydroxyflavone[9] by refluxing with glacial acetic acid and sodium acetate.

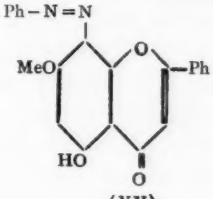
Chrysin[12] was partially methylated to tectochrysin (XIV) by treatment with one mole of dimethyl sulphate in acetone solution in the presence of potassium carbonate. Tectochrysin (XIV) coupled with benzenediazonium



(XIII)

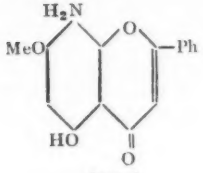


(XIV)

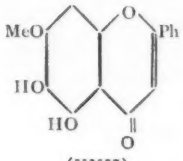


(XV)

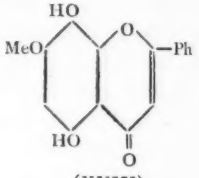
chloride to form a monoazo dye, formulated as 8-benzeneazotectochrysin (XV), by analogy with the behaviour of 5-hydroxyflavone. Reduction of (XV) with zinc dust in alcohol-acetic acid yielded the amine (XVI). The diazonium salt from (XVI) was even more difficult to decompose than that from (III), prolonged boiling with 80% sulphuric acid being necessary. Under these conditions, some general decomposition was unavoidable and the product, which gave all the characteristic colour reactions of baicalein, could not be isolated in pure crystalline form. However, on boiling the amine (XVI) with 32% hydrochloric acid for 24 hours,[13] baicalein 7-methyl ether (XVII), agreeing in all its properties with the substance described by Sastri and Seshadri,[14] was obtained in good yield. Thus treatment with hydrochloric



(XVI)



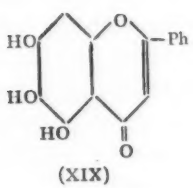
(XVII)



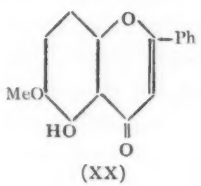
(XVIII)

acid resulted in hydrolysis of the amine, accompanied by a rearrangement of 5:8-dihydroxy-7-methoxyflavone (XVIII) to 5:6-dihydroxy-7-methoxyflavone (XVII). Demethylation of (XVII) yielded baicalein (XIX), which was first isolated from a natural source by Shibata, Nakamura and Iwata,[15] but synthesized earlier by Bargellini.[16] A more recent synthesis is due to Sastri and Seshadri.[17]

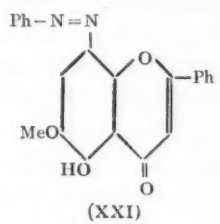
5-Hydroxy-6-methoxyflavone (XX) was prepared by methylating 5:6-dihydroxyflavone with one mole of dimethyl sulphate in acetone in the



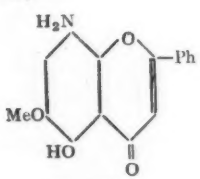
(XIX)



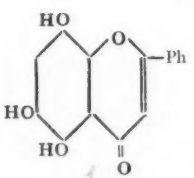
(XX)



(XXI)



(XXII)



(XXIII)

presence of potassium carbonate[18]; and also by partially demethylating 5:6-dimethoxyflavone with aluminium chloride in ether at room temperature.[4] With diazotized aniline, (XX) gave 8-benzeneazo-5-hydroxy-6-methoxyflavone (XXI), which was reduced to the amine (XXII). When the amine was treated for 24 hours with boiling 32% hydrochloric acid[13] and the product, which did not contain nitrogen, was acetylated, the acetyl derivative on hydrolysis with alcoholic hydrochloric acid yielded 5:6:8-trihydroxyflavone (XXIII) prepared by Rajagopalan, Seshadri and Varadarajan by a different route.[18]

Experimental

6-Benzoyloxy-2-hydroxydibenzoylmethane (XII)

2-Acetylresorcinol dibenzoate (2 g.)[9] was added to a solution of sodium ethoxide (from 0·6 g. of sodium) in absolute alcohol (40 c.c.). The mixture was frequently shaken until the ester completely went into solution (1 hr.). There was a rapid change of the colour of the solution from pale yellow to green. On leaving overnight at room temperature the reaction mixture set to a dark greenish brown gel, which was acidified with ice-cold dilute acetic acid. After 4 hours the crystalline precipitate was filtered and crystallized from aqueous alcohol. The mixture of plates and needles (0·71 g.) melted at 124° (Found: C, 72·9; H, 4·3. $C_{22}H_{16}O_5$ requires C, 73·3; H, 4·4%). The alcoholic solution develops a reddish brown colour with ferric chloride.

The filtrate after separation of the crude diketone deposited a brown precipitate (0·1 g.) which crystallized from alcohol in colourless needles, m.p. 157°, undepressed when mixed with 5-hydroxyflavone.

5-Hydroxyflavone

6-Benzoyloxy-2-hydroxydibenzoylmethane (1·4 g.) was refluxed for 5 hours with glacial acetic acid (15 c.c.) containing fused sodium acetate (3 g.). The product was poured into water and the brown precipitate crystallized from alcohol in needles (1 g.), m.p. 157°.

2 : 6-*Dihydroxytribenzoylmethane* (*XIII*)

(*a*) 2-Acetylresorcinol dibenzoate (2 g.) was dissolved in dry ether (40 c.c.) in a pressure bottle. Finely powdered sodamide (3 g.) was added, the bottle stoppered and mechanically shaken for 6 hours. The light green precipitate was filtered and cautiously added to ice-cold dilute acetic acid. The yellow precipitate was collected and crystallized successively from benzene and from ethyl acetate. The yellow elongated plates melted at 180–81° (Found: C, 73·4; H, 4·4. $C_{22}H_{16}O_5$ requires C, 73·3; H, 4·4%).

(*b*) 2-Acetylresorcinol dibenzoate (2 g.) was dissolved in dry benzene (20 c.c.), finely powdered sodamide (3 g.) added and the mixture refluxed for 6 hours. The pale green product was filtered, washed with benzene, sucked dry, and gradually stirred into ice-cold dilute acetic acid. Successive crystallization of the yellow precipitate (1 g.) from benzene and from ethyl acetate gave yellow plates, m.p. 181°. The m.p. was not depressed by mixing with the product obtained by method (*a*), but when mixed with 3-benzoyl-5-hydroxyflavone prepared according to Baker,[9] the m.p. was 160–65°. The alcoholic solution gives a deep brownish purple colour with ferric chloride.

3-*Benzoyl*-5-*hydroxyflavone*

A solution of the triketone from the previous experiment (0·5 g.) in glacial acetic acid (5 c.c.) containing fused sodium acetate (1 g.) was refluxed for 6 hours and poured into water. The product crystallized from a mixture of alcohol and acetic acid in yellow rods (0·4 g.), m.p. 178–79°, undepressed when mixed with 3-benzoyl-5-hydroxyflavone prepared according to Baker.[9]

8-*Benzeneazo*-5-*hydroxyflavone* (*II*)

A solution of benzenediazonium chloride, prepared as usual from aniline (2 g., 2·5 mol.), hydrochloric acid (32%, 6 c.c.), alcohol (30 c.c.) and sodium nitrite (1·8 g. in 10 c.c. water) was gradually added at 0° to a solution of 5-hydroxyflavone (2 g.) in alcohol (80 c.c.), pyridine (14 c.c.), 20% aqueous caustic soda (2 c.c.) and ammonia (*d.* 0·88; 2 c.c.). During addition of the diazonium solution and for 6 hours thereafter, the mixture was mechanically stirred and maintained at 0°. It was then left overnight in a refrigerator and the brown precipitate that separated was collected, boiled with 10% hydrochloric acid for a few minutes, filtered and crystallized from acetic acid. The orange plates (1·5 g.) melted at 214–15° (Found: N, 8·2. $C_{21}H_{14}O_3N_2$ requires N, 8·2%). The alcohol solution gives a reddish brown colour with ferric chloride, and a deep red coloration with aqueous sodium hydroxide. Acetylation of the dye in the usual manner with acetic anhydride and pyridine gave the *acetyl* derivative, which crystallized from alcohol in orange-yellow needles, m.p. 186° (Found: N, 7·5. $C_{23}H_{16}O_4N_2$ requires N, 7·3%).

8-*Benzeneazo*-5-*methoxyflavone*

8-Benzeneazo-5-hydroxyflavone (1 g.), dissolved in boiling anhydrous acetone (20 c.c.) was treated with dimethyl sulphate (1·25 g.) and freshly ignited potassium carbonate (4 g.) during 15 hours. On pouring into water and removal of acetone on the water-bath, the product crystallized from

glacial acetic acid in orange plates, m.p. 206–08°, depressed to 172–80° when mixed with 8-benzeneazo-5-hydroxyflavone (Found: N, 7·9. $C_{22}H_{16}O_3N_2$ requires N, 8·0%). The yellow alcoholic solution gives no colour with ferric chloride or aqueous caustic soda.

8-Amino-5-hydroxyflavone (III)

8-Benzeneazo-5-hydroxyflavone (1 g.) suspended in a boiling mixture of alcohol (80 c.c.) and acetic acid (10 c.c.) was treated under reflux with zinc dust (2 g.). There was a vigorous reaction, the red solid gradually dissolved and the red solution became orange yellow in colour. Boiling was continued 10 minutes longer, the hot solution was filtered, and the zinc was extracted thrice with 5 c.c. portions of hot alcohol. The filtrate was cooled and diluted with water. The compound that separated was filtered and crystallized from dilute alcohol. The brownish yellow rods (0·6 g.) melted at 204–05° (Found: N, 5·7. $C_{15}H_{11}O_3N$ requires N, 5·5%). The orange yellow alcoholic solution turns dark greenish brown on the addition of a drop of alcoholic ferric chloride. The compound is insoluble in aqueous caustic soda, and gives a yellow solution in conc. sulphuric acid.

5-Hydroxyflavone-8-diazonium sulphate and 5: 6-dihydroxyflavone

8-Amino-5-hydroxyflavone (0·1 g.) was suspended in a mixture of water (10 c.c.) and conc. sulphuric acid (0·5 c.c.). On boiling the mixture, the orange compound became colourless and gradually dissolved. The mixture was filtered and the small amount of residue extracted again with a mixture of water (10 c.c.) and concentrated sulphuric acid (0·5 c.c.). The combined filtrates on cooling deposited the amine sulphate as microscopic needles. The suspension was cooled to 5° and sodium nitrite (0·04 g.) in water (1 c.c.) was added with stirring. The crystals first became reddish brown, but completely went into solution in 10 minutes, giving a clear, pale brown solution. After 20 minutes, excess nitrous acid was destroyed by the addition of urea and the diazonium solution gradually added to a boiling mixture of water (20 c.c.) and concentrated sulphuric acid (10 c.c.). After the addition, a drop of the boiling mixture was tested every 5 minutes with alkaline β-naphthol for the presence of the diazonium salt. When the volume of the boiling mixture decreased to about 15 c.c., there was a vigorous effervescence due to evolution of nitrogen, the orange-yellow colour of the solution changed to brown, and the solution failed to give a red colour with alkaline β-naphthol indicating complete hydrolysis of the diazonium salt. The mixture was cooled and added to ice and water. The brownish yellow precipitate was collected, washed with water and crystallised from dilute alcohol (norit). The yellow needles (0·03 g.) melted at 188–90°, not

depressed by mixing with an authentic sample of 5:6-dihydroxyflavone prepared from 6-hydroxyflavone.[1]

On acetylation by refluxing with acetic anhydride and pyridine, 5:6-diacetoxyflavone, m.p. 166–67°, was obtained.

5-Hydroxyflavone-8-azo-β-naphthol, prepared by coupling alkaline β-naphthol with diazotized 8-amino-5-hydroxyflavone, crystallized from nitrobenzene in elongated plates, m.p. 288–90° (Found: N, 6·4. $C_{25}H_{16}O_4N_2$ requires N, 6·9%).

3-Acetyl-2-hydroxy-4-methoxyazobenzene (VIII)

2-Acetyl-4-benzeneazoresorcinol (0·5 g.), dimethyl sulphate (0·25 g., 1 mol.) and freshly ignited potassium carbonate (1 g.) in benzene were heated under reflux for 8 hours. The reaction mixture was diluted with water and the benzene layer extracted 4 times with 5% aqueous caustic soda. Acidification of the alkaline extract gave an orange substance which crystallized from alcohol in needles, m.p. 90° (Found: N, 10·1. $C_{15}H_{14}O_3N_2$ requires N, 10·4%). The alcoholic solution gives a pale reddish brown colour with ferric chloride. The solution in conc. sulphuric acid is pale orange in colour.

After extraction with alkali, the benzene layer was evaporated to dryness; the residual dimethyl ether crystallized from alcohol in orange plates, m.p. 110° with previous shrinking (Found: N, 10·3. $C_{16}H_{16}O_3N_2$ requires N, 9·9%).

3-Acetyl-4-hydroxy-2-methoxyazobenzene (VII)

A solution of benzenediazonium chloride prepared from aniline (0·6 g., 1 mol.) was gradually added to a solution of 2-acetylresorcinol monomethyl ether (1·1 g.) in alcohol (40 c.c.) and pyridine (6 c.c.) at 0°. The mixture was left overnight in a refrigerator, and the light orange precipitate collected, treated with hydrochloric acid to remove pyridine, washed and crystallised from alcohol. The orange needles (1 g.) melted at 100° with shrinking at 97° (Found: N, 10·7. $C_{15}H_{14}O_3N_2$ requires N, 10·4%). The alcoholic solution gives a deep brown colour with ferric chloride.

8-Benzeneazo-5-hydroxyflavone (II)

3-Acetyl-4-hydroxy-2-methoxyazobenzene (2·3 g.) was intimately mixed with benzoic anhydride (36 g.) and sodium benzoate (12 g.) and heated at 180–90° for 10 hours. Hydrolysis was effected by means of caustic potash (22 g.) in alcohol (240 c.c.) on the water-bath for 40 minutes. Alcohol was removed under reduced pressure, the residue diluted with water and saturated with carbon dioxide. The orange yellow precipitate was filtered, washed

with water and crystallized from acetic acid. The orange plates (1·9 g.) melted at 215°, not depressed by admixture with 8-benzeneazo-5-hydroxyflavone obtained by coupling 5-hydroxyflavone with benzene diazonium chloride.

6-Benzeneazo-5-hydroxyflavone (*V*)

2-Acetyl-4-benzeneazoresorcinol (4 g.) was intimately mixed with benzoic anhydride (60 g.) and sodium benzoate (10 g.) and heated at 180–90° for 10 hours. The reddish brown product was treated on the water-bath with alcohol (300 c.c.) and caustic potash (34 g. in 40 c.c. water) during 40 minutes. Most of the alcohol was removed under reduced pressure, the residue diluted with water and saturated with carbon dioxide. The reddish brown precipitate was filtered, washed with water and crystallized from acetic acid. The orange-yellow rods (3 g.) melted at 210°, lowered to 170–88° when mixed with 8-benzeneazo-5-hydroxyflavone (II) (Found: N, 8·4. $C_{21}H_{14}O_3N_2$ requires N, 8·2%). The alcoholic solution gives a reddish brown colour with ferric chloride. The *acetyl* derivative crystallized from alcohol in light orange needles, m.p. 195° (Found: N, 7·6. $C_{23}H_{16}O_4N_2$ requires N, 7·3%).

6-Benzeneazo-5-hydroxyflavone was subjected to methylation under the conditions used for methylating compound (II). The product crystallized from acetic acid in orange rods, m.p. 206°, not depressed by mixing with 6-benzeneazo-5-hydroxyflavone. Methylation therefore had not taken place.

6-Amino-5-hydroxyflavone (*VI*)

6-Benzeneazo-5-hydroxyflavone (1 g.) in boiling alcohol (60 c.c.) and acetic acid (10 c.c.) was treated with zinc dust (2 g.). The orange red solution changed to a deep brownish grey. More zinc dust (0·5 g.) was added, the mixture refluxed for 10 minutes longer, filtered hot, and the residue extracted thrice with 5 c.c. portions of hot alcohol. The filtrate was diluted with water and the yellow precipitate collected and crystallized by dissolving in hot alcohol (Norit), diluting to slight turbidity and cooling. The yellow elongated plates (0·6 g.) melted at 181° with previous shrinking (Found: N, 5·7. $C_{15}H_{11}O_3N$ requires N, 5·5%). Sugasawa describes the amine as golden yellow plates melting at 177°.[2] The alcoholic solution turns an intense reddish brown with ferric chloride. With concentrated sulphuric acid, a yellow solution is obtained. The substance does not dissolve in aqueous caustic soda.

Conversion of 6-amino-5-hydroxyflavone into 5:6-dihydroxyflavone

6-Amino-5-hydroxyflavone (0·3 g.) was boiled with water (30 c.c.) and sulphuric acid (98%; 3 c.c.). The yellow crystals changed to white and

then dissolved. On cooling, colourless crystals of the amine sulphate were deposited. On addition of sodium nitrite (0·5 g.), the crystals gradually disappeared, and a yellow precipitate of the diazo-oxide then separated. This was filtered, washed with water and dried (Found: N, 9·6. $C_{15}H_8O_3N_2$ requires N, 10·6%).

A suspension of the diazo-oxide from 0·3 g. of the amine was added to a boiling mixture of water (30 c.c.) and 98% sulphuric acid (30 c.c.). The brownish yellow solution was boiled to about 45 c.c., when there was a vigorous evolution of nitrogen and the dark orange brown solution gave no indication of coupling with alkaline β-naphthol. The brown precipitate obtained on cooling crystallized from dilute alcohol in yellow needles (0·1 g.), m.p. 188–89°, not altered when mixed with 5: 6-dihydroxyflavone.[1] On acetylation in the usual way 5: 6-diacetoxyflavone melting at 166° was obtained.

Action of hydrochloric acid on 8-amino-5-hydroxyflavone (III)

8-Amino-5-hydroxyflavone (0·1 g.) was treated with boiling 16% hydrochloric acid (20 c.c.) for 20 hours. The deep brown precipitate was collected and identified as an amine hydrochloride, m.p. 230–35°. Treatment with aqueous sodium bicarbonate, and crystallization from dilute alcohol gave yellow elongated plates (0·06 g.) which melted at 178°, not depressed by mixing with 6-amino-5-hydroxyflavone. A further quantity of this amino-hydroxyflavone was recovered by neutralizing the hydrochloric acid filtrate with sodium bicarbonate.

6-Amino-5-hydroxyflavone was recovered unchanged by treatment with boiling 16% hydrochloric acid for 20 hours, followed by neutralization with sodium bicarbonate.

Action of hydrochloric acid on primetin (I)

A solution of primetin (0·05 g.) in alcohol (1 c.c.) and 32% hydrochloric acid (3 c.c.) was refluxed for 20 hours and poured into water. The yellow precipitate crystallized from dilute alcohol in needles, m.p. 189°, not depressed by admixture with 5: 6-dihydroxyflavone prepared from 6-hydroxyflavone.[1] The substance also exhibited all the reactions of 5: 6-dihydroxyflavone.

Action of 80% sulphuric acid on primetin

Primetin (0·05 g.) was refluxed with 98% sulphuric acid and water (5 c.c.) for 45 minutes. After cooling and diluting with water, the yellow precipitate was collected and crystallized from dilute alcohol. The yellow needles shrank at 170° and melted at 180–85°, and gave all the reactions of 5: 6-dihydroxyflavone.

3-*Benzeneazo*-2: 6-*dihydroxyphenyl styryl ketone* (*IX*)

2-Acetyl-4-benzeneazoresorcinol (1·06 g.) and benzaldehyde (1·3 g., 3 mols.) in absolute alcohol (20 c.c.) were treated with caustic potash (15 g. in 20 c.c. water), and left overnight at room temperature. The reaction mixture was added to crushed ice and hydrochloric acid. The bright red precipitate crystallized from glacial acetic acid in deep red plates, m.p. 178° (Found: N, 7·9. $C_{21}H_{16}O_3N_2$ requires N, 8·1%).

8-*Benzeneazo*-3-*benzoyl*-5-*hydroxyflavone*

A solution of benzenediazonium chloride prepared from aniline (0·3 g.) was gradually added to a solution of 3-benzoyl-5-hydroxyflavone (0·3 g.) in alcohol (15 c.c.), pyridine (2 c.c.), caustic soda (0·3 c.c. of 20% solution) and ammonia (*d.* 0·88; 0·3 c.c.) at 0°. On leaving overnight in a refrigerator, the brown precipitate was collected and crystallized from acetic acid. The orange needles (0·15 g.) melted at 247–49° (Found: N, 6·6. $C_{28}H_{18}O_4N_2$ requires N, 6·3%). The *acetyl* derivative crystallized from alcohol in needles, m.p. 184° (Found: N, 5·9. $C_{30}H_{20}O_5N_2$ requires N, 5·7%).

8-*Benzeneazotectochrysin* (*XV*)

Benzenediazonium chloride from aniline (1 g.) was gradually added to a solution of tectochrysin (0·8 g.) in pyridine (12 c.c.), alcohol (60 c.c.), 5 N caustic soda solution (0·75 c.c.) and ammonia (*d.* 0·88; 1·2 c.c.) at 0°. On leaving overnight in a refrigerator, the orange precipitate was filtered, treated with hydrochloric acid (32%) in which it partly dissolved and diluted with water. The red precipitate crystallized from acetic acid in orange needles (0·6 g.), m.p. 232° (Found: N, 7·6. $C_{22}H_{16}O_4N_2$ requires N, 7·8%). The substance gives an orange solution with conc. sulphuric acid and a brown colouration with alcoholic ferric chloride.

8-*Benzeneazo*-5: 7-*dimethoxyflavone*

8-Benzeneazotectochrysin (0·1 g.), dry acetone (10 c.c.), dimethyl sulphate (0·5 g.) and freshly ignited potassium carbonate (2 g.) were heated for 15 hours on a water-bath. The product was poured into water, excess acetone removed on a water-bath and the precipitate crystallized from alcohol. The orange needles melted at 207–08° (Found: N, 7·8. $C_{23}H_{18}O_4N_2$ requires N, 7·3%). The substance gives no ferric chloride reaction and is insoluble in aqueous caustic soda.

8-*Aminotectochrysin* (*XVI*)

8-Benzeneazotectochrysin (1 g.) in boiling alcohol (60 c.c.) and glacial acetic acid (10 c.c.) was treated with zinc dust (2·0 g.). After 10 minutes,

when the colour of the solution had become orange, zinc was filtered off and extracted thrice with 5 c.c. portions of boiling alcohol. Dilution of the filtrate and extracts with water gave an orange-yellow precipitate, which crystallized from dilute alcohol in fine yellow needles (0·7 g.) and melted at 197° with previous shrinking (Found: N, 4·7. $C_{16}H_{13}O_4N$ requires N, 4·9%). The alcoholic solution develops a brown colouration with ferric chloride. With aqueous sodium hydroxide the aminophenol turns red, but does not dissolve. It dissolves in hot hydrochloric acid and sulphuric acid, the colourless salts being deposited on cooling. On the addition of sodium nitrite, the salts gradually dissolve leaving a trace of a fluffy residue and the diazonium salts couple with alkaline β-naphthol to form a brownish red dye.

Baicalein 7-methyl ether (*XVII*)

8-Aminotectochrysin (0·8 g.) was refluxed for 24 hours with 25% hydrochloric acid (45 c.c.) and the mixture filtered hot. The residue was washed with hot water, and crystallization from alcohol gave yellow plates (0·4 g.), m.p. 219° (Found: C, 67·4; H, 4·3. $C_{16}H_{12}O_5$ requires C, 67·6; H, 4·3%). A deep green colour similar to that produced with 5:6-dihydroxyflavone is produced when a drop of ferric chloride is added to an alcoholic solution of the substance. With aqueous caustic soda it develops an orange-red colour and a greenish brown precipitate then separates. With sodium amalgam in absolute alcohol, a transient orange colour appears which rapidly changes to a dark greenish blue; after some minutes a brown precipitate is formed. With conc. sulphuric acid a yellow non-fluorescent solution is obtained. An alcoholic solution gives an orange yellow precipitate with alcoholic lead acetate. All these properties agree with those recorded by Sastri and Seshadri[14] for baicalein 7-methyl ether.

5:6-*Diacetoxy-7-methoxyflavone*

Baicalein 7-methyl ether (0·1 g.) was acetylated in the usual manner; the diacetyl derivative crystallized from alcohol in colourless plates, m.p. 239–40° (Found: C, 65·3; H, 4·5. $C_{20}H_{16}O_7$ requires C, 65·2; H, 4·3%).

5:6:7-*Trimethoxyflavone*

Baicalein 7-methyl ether (0·1 g.) was treated for 8 hours with boiling acetone (20 c.c.), dimethyl sulphate (0·5 c.c.) and freshly ignited potassium carbonate (1 g.). On dilution with water and removal of acetone on a water-bath, the trimethyl ether separated as a crystalline solid which crystallized from dilute alcohol in narrow rectangular plates, m.p. 166° (Seshadri *et al.*,[14–17] quote the m.p. 165–66°).

Baicalein (*XIX*)

The 7-methyl ether (0·1 g.) was treated with boiling hydriodic acid (*d.* 1·5; 4 c.c.) and acetic anhydride (4 c.c.) for 4 hours. On pouring into saturated sodium bisulphite solution, the yellow precipitate was collected and crystallized from dilute alcohol. The yellow plates melted at 264° and gave all the reactions described by Seshadri[17] and others[15, 16] for baicalein (Found: C, 66·6; H, 3·7. $C_{15}H_{10}O_5$ requires C, 66·7; H, 3·7%).

8-*Benzeneazo*-5-*hydroxy*-6-*methoxyflavone* (*XXI*)

Benzenediazonium chloride prepared from aniline (1 g.) was gradually added to a solution of 5-hydroxy-6-methoxyflavone (0·8 g.) in alcohol (60 c.c.), pyridine (12 c.c.), 5 N caustic soda (0·6 c.c.) and ammonia (*d.* 0·88; 2 c.c.) at 0°. The orange dye crystallized from acetic acid in dull orange elongated plates (0·5 g.), m.p. 233–34° (Found: N, 7·8. $C_{22}H_{16}O_4N_2$ requires N, 7·9%). A reddish brown colour is developed when a drop of ferric chloride is added to its alcoholic solution. It gives an orange solution with alcoholic caustic soda and a scarlet solution with conc. sulphuric acid.

8-*Amino*-5-*hydroxy*-6-*methoxyflavone* (*XXII*)

8-Benzeneazo-5-hydroxy-6-methoxyflavone (0·5 g.) in a boiling mixture of alcohol (60 c.c.) and acetic acid (10 c.c.) was treated with zinc dust (2 g.) during 15 mins. Worked up as described earlier, the amine crystallized from dilute alcohol in brown elongated plates (0·3 g.), m.p. 210° (Found: N, 5·2. $C_{16}H_{13}O_4N$ requires N, 4·9%). An alcoholic solution gives with ferric chloride a green colouration, changing to greenish brown. The solution in conc. sulphuric acid is yellow.

Hydrolysis of 8-*amino*-5-*hydroxy*-6-*methoxyflavone*: 5:6:8-*Trihydroxyflavone* (*XXIII*)

The amine (XXII; 0·2 g.) was refluxed with 32% hydrochloric acid (20 c.c.) for 24 hours, when the diazotization test was negative. On cooling the yellowish brown precipitate (0·15 g.) was collected, dried and acetylated by refluxing with acetic anhydride (10 c.c.) and pyridine (1 c.c.) for 2 hours. The product was poured on crushed ice and the precipitate of 5:6:8-triacetoxyflavone crystallized from alcohol. The shining rectangular plates melted at 217° (Rajagopalan *et al.*[18] quote m.p. 214°) (Found: C, 63·2; H, 4·3. $C_{21}H_{16}O_8$ requires C, 63·6; H, 4·0%).

The acetyl derivative (0·05 g.) was hydrolysed by heating with alcohol (10 c.c.) and 32% hydrochloric acid (2 c.c.) for 30 mins. The solution was diluted and excess alcohol removed under vacuum. The orange yellow

product crystallized from dilute alcohol in sheaves of yellow needles, m.p. 236° (Found: C, 67.4; H, 4.0. $C_{15}H_{10}O_5$ requires C, 66.7; H, 3.7%). It gives a brown colour with alcoholic ferric chloride and a red solution with aqueous caustic soda which becomes paler and finally yellow on standing. These properties are in agreement with those described by Rajagopalan *et al.*[18]

SUMMARY

The coupling of 5-hydroxyflavone with benzenediazonium chloride led to an azo dye which was different from the compound obtained by the Robinson flavone condensation on 2-acetyl-4-benzeneazoresorcinol and benzoic anhydride. The two compounds are shown to be the 8- and 6-benzeneazo derivatives of 5-hydroxyflavone respectively. The conversion of both the azo dyes into 5:6-dihydroxyflavone is described.

Tectochrysin was converted to baicalein 7-methyl ether by coupling with benzenediazonium chloride, followed by reduction of the azo dye to the amine and treatment of the latter with hydrochloric acid. Baicalein was obtained by demethylation of the 7-methyl ether. The same series of reactions carried out on 5-hydroxy-6-methoxyflavone[25] led to 5:6:8-trihydroxyflavone.

Our thanks are due to Dr. T. S. Gore for carrying out the microanalyses recorded in the paper.

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CHEMOTHERAPY OF MALARIA

Part VII. Phenylene-Diguanidine Derivatives

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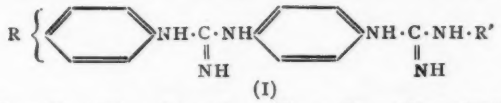
In view of the fact that some guanidine derivatives show distinct antimalarial activity[1] and that paludrine is also a biguanide, it was thought worthwhile to prepare and test compounds of general formula (I), with two guanidine groups separated by a benzene ring. Compounds of this type in which one of the guanidine residue is replaced by amidine residues have been prepared



(I)

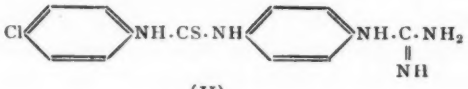
where R = H, *o*.Cl; *m*.Cl; *p*.Cl; *m*.Br; *p*.Br; *o*.Me; *m*.Me; *p*.Me; *o*.MeO; *p*.MeO.
R′ = H; isoPropyl–; *n*.Butyl.

by the English workers and found to be devoid of activity.[2] Since this work was started, compounds of type (I) have been prepared by Safer and Kushner[3] and some of these have been reported to possess trypanocidal activity.

Attempts were first made to work out a general method for the synthesis of a compound (I, R = Cl; R′ = H), so that this could be used to synthesise series of the type (I). *p*-Aminophenylguanidine did not react with either *p*-chlorophenylcyanamide or S-methyl-*p*-chlorophenylisothioureas hydroiodide. This is not unexpected because the free amino group in *p*-aminophenylguanidine has been found[4] not to react with S-methyl-isothiourea sulphate to furnish the diguanidine derivative. The same negative results were obtained by using *p*-aminophenylthiourea in place of *p*-aminophenylguanidine. On the other hand, *p*-aminophenylguanidine and *p*-aminophenylthiourea condensed with *p*-chlorophenylisothiocyanate to furnish respectively-4 (4′-chlorophenylthioureido) phenyl guanidine (II) and 4 (4′ chlorophenylthioureido) phenyl phenylthiourea (III).

S-Methyl-*p*-chlorophenylisothiourea hydriodide reacted with *p*-phenylenediamine to furnish 4 (4′-chlorophenylguanidino) aniline (IV) which could also be prepared by the action of *p*-chloro phenylcyanamide on acetphenylenediamine and hydrolysing the resulting acetaminoguanidine derivative.[5] The

guanidine derivative (IV) obtained did not react with S-methylisothiourea sulphate to furnish the diguanidine but on the other hand with thiocyanic acid yielded 4 (4′-chlorophenylguanidino) phenyl thiourea (V). The best method of converting these thiourea and dithiourea derivative into guanidines proved to be to treat the S-methyl derivatives with ammonia. Treatment of the dithiourea derivatives with alcoholic ammonia and mercuric oxide furnished the corresponding diurea derivative instead of the diguanidine.



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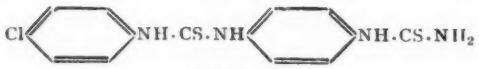

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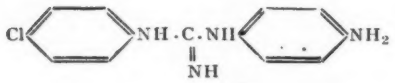

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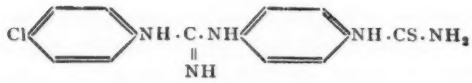
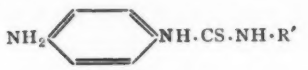
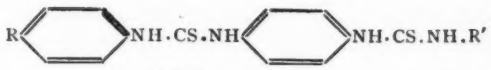


(V)

In view of the above observations, the following general method was adopted to prepare a series of diguanidinophenyl derivatives of formula (I). The thiourea derivatives (VI, wherein R′ = H, isoPr, *n*.Bu) were prepared (Table I) by the methods described in the experimental part. These thioureas were in turn condensed with a number of isothiocyanates to furnish the dithioureas of formula (VII), which are listed in Table II. These dithioureas reacted with two molecular equivalents of methyliodide to yield the di-S-methyl derivatives (Table III) which by the prolonged action of ammonia furnished the guanidine derivatives of formula (I); The compounds obtained are presented in Table IV.



(VI)



(VII)

Eleven compounds (Nos. 63, 66, 68, 70, 71, 72, 75, 76, 78, 79 and 82) were tested for their antimalarial action on *Plasmodium berghi* in mice and were found to be devoid of activity.

TABLE I

Phenylthioureas

$R^1-C_6H_4-NH.CS.NH.R^2$

Serial No.	R^1	R^2	Molecular Formula	M.P./°C.	Nitrogen % Req.	Found
1	Acetamino-	H-	$C_9H_{11}N_3OS$	211–12	20·09	20·07
2	Acetamino-	*iso*-Propyl-	$C_{12}H_{17}N_3OS$	212–	16·73	16·71
3	Acetamino-	*n*-Butyl	$C_{13}H_{19}N_3OS$	185–86	15·09	15·23
4	Acetamino-	Di-ethyl-	$C_{13}H_{19}N_3OS$	213–14	15·85	16·10
5	Acetamino-	*p*-Chlorophenyl-	$C_{15}H_{14}N_3OSCl$	202–	13·01	13·14
6	Nitro-	*iso*-Propyl-	$C_{10}H_{13}N_3O_2S$	197–98	17·80	17·50
7	Amino-	H-[1]	$C_7H_9N_3S$	201–02	25·14	25·00
8	Amino-	*iso*-Propyl-[2]	$C_{10}H_{15}N_3S$	147–48	20·08	20·36
9	Amino-	*n*-Butyl-[3]	$C_{11}H_{17}N_3S$	123–24	18·83	19·01
10	Amino-	*p*-Chlorophenyl-	$C_{13}H_{12}N_3SCl$	241–43	15·19	14·91

1. Hydrochloride, m.p. 278-80° ; Picrate, m.p. 190-92°.
2. Hydrochloride, m.p. 231° (dec.); Picrate, m.p. 129–31°.
3. Hydrochloride, m.p. 238° ; Picraté, m.p. 166°.

EXPERIMENTAL

Isothiocyanates.—These were prepared according to the standard method by the action of carbon disulphide on the amines in ammonium or sodium hydroxide solution, the ammonium or the sodium salt of the dithioformic acid formed in the reaction dissolved in water, treated with a solution of copper sulphate and steam distilled or extracted with a solvent. Thus were prepared: isopropyl-, *n*-butyl-, phenyl-, *p*-chlorophenyl-, *m*-chlorophenyl-*o*-chlorophenyl-, *m*-bromophenyl-, *p*-bromophenyl-, *o*-tolyl-, *m*-tolyl-, *p*-tolyl-*o*-methoxyphenyl-, *p*-methoxyphenyl-isothiocyanates. *p*-Acetaminophenyl-isothiocyanate had m.p. 198–99° (Found: N, 14·58. $C_9H_{11}N_2OS$ requires N, 14·56%).

Phenylthioureas.—The various derivatives listed in Table I were prepared by the action of different isothiocyanates on the appropriate amines in an inert solvent. 2:4-dinitroaniline and *p*-acetaminophenylisothiocyanate did not react to furnish the thiourea derivative.

N-p-Nitrophenyl-N'-isopropylthiourea (*No.* 6).—A mixture of *p*-nitroaniline (13·9 g.) and isopropylisothiocyanate (12·1 g.) was heated in an oil-bath at 130° for 30 minutes and then at 150° for 30 minutes. The reaction mixture was cooled and diluted with ether, where by the thiourea derivative crystallised out in needles (yield, 15 g.). It was recrystallised from alcohol.

TABLE II

N^1-aryl-N^2-(p-alkylthiocarbamido)-phenylthioureas

R^1–NH–CS–NH–C$_6$H$_4$–NH–CS–NH–R^2

Serial No.	R^1	R^2	Molecular Formula	M.P.*/°C.	Nitrogen % Req.	Found
11	H-	*iso*-Propyl-	$C_{11}H_{16}N_4S_2$	200–01	20·89	20·79
12	Phenyl-	*iso*-Propyl-	$C_{17}H_{19}N_4S_2$	189–90	16·32	16·50
13	Phenyl-	*n*-Butyl-	$C_{18}H_{21}N_4S_2$	195–96; 214–17	15·65	15·51
14	*p*-Chlorophenyl-	H-	$C_{14}H_{13}N_4S_2Cl$	237–39;	16·64	16·49
15	*p*-Chlorophenyl-	*iso*-Propyl-	$C_{17}H_{19}N_4S_2Cl$	190–91; 214–17	14·83	14·48
16	*p*-Chlorophenyl-	*n*-Butyl-	$C_{18}H_{21}N_4S_2Cl$	219–21	14·26	14·00
17	*o*-Chlorophenyl-	*iso*-Propyl-	$C_{17}H_{19}N_4S_2Cl$	197–98. above 290	14·83	15·25
18	*o*-Chlorophenyl-	*n*-Butyl-	$C_{18}H_{21}N_4S_2Cl$	192–93; 211–13	14·26	14·21
19	*m*-Chlorophenyl-	*iso*-Propyl-	$C_{17}H_{19}N_4S_2Cl$	187–88; 205–06	14·83	15·09
20	*m*-Chlorophenyl-	*n*-Butyl-	$C_{18}H_{21}N_4S_2Cl$	181–83; 215–17	14·26	13·88
21	*p*-Bromophenyl-	*iso*-Propyl-	$C_{17}H_{19}N_4S_2Br$-	214–18	13·27	13·36
22	*p*-Bromophenyl-	*n*-Butyl-	$C_{18}H_{21}N_4S_2Br$-	219–20	12·81	12·88
23	*m*-Bromophenyl-	*iso*-Propyl-	$C_{17}H_{19}N_4S_2Br$	171–72; 197–98	13·27	13·29
24	*m*-Bromophenyl-	*n*-Butyl-	$C_{18}H_{21}N_4S_2Br$	179–80; 215–19	12·81	12·45
25	*p*-Tolyl-	*iso*-Propyl-	$C_{18}H_{21}N_4S_2$	168–70	15·68	16·01
26	*p*-Tolyl-	*n*-Butyl-	$C_{19}H_{23}N_4S_2$	195–96; 215–17	15·04	15·17
27	*m*-Tolyl-	*iso*-Propyl	$C_{18}H_{21}N_4S_2$	172–73; 209–12	15·68	15·50
28	*m*-Tolyl-	*n*-B-Pyl-	$C_{19}H_{23}N_4S_2$	176–77; 215–18	15·04	14·85
29	*o*-Tolyl-	*iso*-Propyl-	$C_{18}H_{21}N_4S_2$	190–91	15·68	15·47
30	*o*-Tolyl-	*n*-Butyl-	$C_{19}H_{23}N_4S_2$	186–87; 214–16	15·04	14·78
31	*p*-Anisyl-	*iso*-Propyl-	$C_{18}H_{21}N_4S_2O$	174–75; 220–21	14·90	14·75
32	*p*-Anisyl-	*n*-Butyl-	$C_{19}H_{23}N_4S_2O$	215–18	14·42	14·59
33	*o*-Anisyl-	*iso*-Propyl-	$C_{18}H_{21}N_4S_2O$	188–90	14·90	14·92
34	*o*-Anisyl-	*n*-Butyl-	$C_{19}H_{23}N_4S_2O$	181–82; 214–18	14·42	14·43
35	*iso*-Propyl-	*iso*-Propyl-	$C_{14}N_{22}N_4S_2$	220–21	18·06	17·87

* Most of the compounds from this series first melt, resolidify and melt again.

N-p-Acetaminophenyl-N'-isopropylthiourea (*No.* 2).—To a boiling solution of *p*-acetaminophenylisothiocyanate (19·2 g.) in acetone (130 c.c.) was added isopropylamine (10 c.c.) and the mixture refluxed for one hour. The crystalline solid that had separated was collected, washed (yield, 23·7 g.) and crystallised from alcohol.

The same compound was obtained by the action of isopropyl isothiocyanate (10·1 g.) on *p*-aminoacetanilide (15·0 g.) in acetone (130 c.c.); Yield, 22 g.

N-p-Aminophenyl-N'-isopropylthiourea (*No.* 8).—This was prepared (i) by the hydrolysis of the abovementioned acetaminothiourea derivative in alco-

TABLE III

Dimethyl derivatives of N^1-aryl-N^2-alkylthiocarbamidophenylthioureas

Serial No.	R^1	R^2	Molecular Formula	M.P./°C.	Nitrogen % Req.	Found
36	H-	*iso*-Propyl	$C_{13}H_{22}N_4S_2I_2$	..	..	..
37	Phenyl-	*iso*-Propyl-	$C_{19}H_{25}N_4S_2I_2$	189–90	..	..
38	Phenyl-	*n*-Butyl-	$C_{20}H_{27}N_4S_2I_2$	185–86	..	..
39	*p*-Chlorophenyl-	H-	$C_{16}H_{19}N_4S_2I_2Cl$	193–94	8·99	8·51
40	*p*-Chlorophenyl-	*iso*-Propyl-	$C_{19}H_{25}N_4S_2I_2Cl$	180–82	8·45	7·88
41	*p*-Chlorophenyl-	*n*-Butyl-	$C_{20}H_{27}N_4S_2I_2Cl$	175–76	..	..
42	*o*-Chlorophenyl-	*iso*-Propyl-	$C_{19}H_{25}N_4S_2I_2Cl$	179–80	..	..
43	*o*-Chlorophenyl-	*n*-Butyl-	$C_{20}H_{27}N_4S_2I_2Cl$	175–76	..	..
44	*m*-Chlorophenyl-	*iso*-Propyl-	$C_{19}H_{25}N_4S_2I_2Cl$	174–76	..	..
45	*m*-Chlorophenyl-	*n*-Butyl-	$C_{20}H_{27}N_4S_2I_2Cl$	173–74	..	..
46	*p*-Bromophenyl-	*iso*-Propyl-	$C_{19}H_{25}N_4S_2I_2Br$	176–77	7·92	7·89
47	*p*-Bromophenyl-	*n*-Butyl-	$C_{20}H_{27}N_4S_2I_2Br$	180–82	..	..
48	*m*-Bromophenyl-	*iso*-Propyl	$C_{19}H_{25}N_4S_2I_2Br$	179–80	7·92	7·93
49	*m*-Bromophenyl-	*n*-Butyl-	$C_{20}H_{27}N_4S_2I_2Br$	176–77	..	..
50	*p*-Tolyl-	*iso*-Propyl-	$C_{20}H_{27}N_4S_2I_2$	187–88	..	..
51	*p*-Tolyl-	*n*-Butyl-	$C_{21}H_{29}N_4S_2I_2$	183–85	..	..
52	*o*-Tolyl-	*iso*-Propyl-	$C_{20}H_{27}N_4S_2I_2$	193–95	..	..
53	*o*-Tolyl-	*n*-Butyl-	$C_{21}H_{29}N_4S_2I_2$	174–75	..	..
54	*m*-Tolyl-	*iso*-Propyl-	$C_{20}H_{27}N_4S_2I_2$	190–92	..	..
55	*m*-Tolyl-	*n*-Butyl-	$C_{21}H_{29}N_4S_2I_2$	172–74	..	
56	*p*-Anisyl-	*iso*-Propyl-	$C_{20}H_{27}N_4S_2I_2O$	186–87	..	
57	*p*-Anisyl-	*n* Bu yl-	$C_{21}H_{29}N_4S_2I_2O$	188–89	..	..
58	*o*-Anisyl-	*iso*-Propyl-	$C_{20}H_{27}N_4S_2I_2O$	186–89	..	..
59	*o*-Anisyl-	*n*-Butyl-	$C_{21}H_{29}N_4S_2I_2O$	175–77	..	..
60	*iso*-Propyl-	*iso*-Propyl	$C_{16}H_{28}N_4S_2I_2$	221–22	..	..

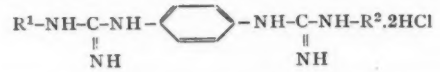
holic hydrochloric acid and (ii) by the catalytic hydrogenation of the corresponding nitroderivative described above with Raney nickel and hydrogen at room temperature at 45 lb.

4 (4′-*Substituted phenylthioureidio*) *phenylthioureas* (*formula VII*).—These compounds were prepared by the action of the isothiocyanates on *p*-aminophenylthioureas in acetone or benzene solution. The dithioureas were thrown out. The compounds obtained are listed in Table II.

N-p-Chlorophenyl-N′-p-isopropylthiocarbamidophenylthiourea (*No.* 15).—*p*-Chlorophenylisothiocyanate (9·3 g.) was added to a clear solution of *p*-aminophenylisopropylthioureas (10·45 g.) dissolved in acetone (100 c.c.). On shaking the flask for about 5 minutes, a bulky precipitate was thrown out.

TABLE IV

N^1-Aryl-N^2-(p-alkylguanido) phenyl-guanidines dihydrochlorides



Serial No.	R^1	R^2	Molecular Formula	M.P./°C.	Nitrogen % Req.	Found	M.P./°C. of Picrate
61	H-	*iso*-Propyl-	$C_{11}H_{20}N_6Cl_2$	208–09	27·36	27·54	212–14
62	Phenyl-	*iso*-Propyl-	$C_{17}H_{24}N_6Cl_2$	265–66	21·93	20·89	210–13
63	Phenyl-	*n*-Butyl-	$C_{18}H_{26}N_6Cl_2$	254–55	21·14	20·94	212–13
64	*p*-Chlorophenyl-	H-	$C_{14}H_{17}N_6Cl_3$	272–73	22·37	22·13	273–74
65	*p*-Chlorophenyl-	*iso*-Propyl-	$C_{17}H_{23}N_6Cl_3$	280–82	20·11	20·32	165–67
66	*p*-Chlorophenyl-	*n*-Butyl-	$C_{18}H_{25}N_6Cl_3$	235–36	19·46	19·06	217–18
67	*o*-Chlorophenyl-	*iso*-Propyl-	$C_{17}H_{23}N_6Cl_3$	279–80	20·11	19·86	130–32
68	*o*-Chlorophenyl-	*n*-Butyl	$C_{18}H_{25}N_6Cl_3$	253	19·46	19·64	120–21
69	*m*-Chlorophenyl-	*iso*-Propyl-	$C_{17}H_{23}N_6Cl_3$	289–90	20·11	20·23	190–92
70	*m*-Chlorophenyl-	*n*-Butyl-	$C_{18}H_{25}N_6Cl_3$	229–30	19·46	19·39	240–45
71	*p*-Bromophenyl-	*iso*-Propyl-	$C_{17}H_{23}N_6Cl_2Br$	265–66	18·18	18·20	..
72	*p*-Bromophenyl-	*n*-Butyl-	$C_{18}H_{25}N_6Cl_2Br$	245–46	17·64	17·32	219–20
73	*m*-Bromophenyl-	*iso*-Propyl-	$C_{13}H_{23}N_6Cl_2Br$	273–74	18·18	18·63	151–52
74	*m*-Bromophenyl-	*n*-Butyl-	$C_{18}H_{25}N_6Cl_2Br$	217–18	17·64	17·83	210–12
75	*p*-Tolyl-	*iso*-Propyl-	$C_{18}H_{26}N_6Cl_2$	260–61	21·14	21·08	118–19
76	*p*-Tolyl-	*n*-Butyl-	$C_{19}H_{28}N_6Cl_2$	255–56	20·48	19·82	209–10
77	*o*-Tolyl-	*iso*-Propyl-	$C_{18}H_{26}N_6Cl_2$	287	21·14	20·60	217–19
78	*m*-Tolyl-	*iso*-Propyl	$C_{18}H_{26}N_6Cl_2$	256–57	21·14	20·80	195–97
79	*m*-Tolyl–	*n*-Butyl-	$C_{19}H_{28}N_6Cl_2$	230–31	20·48	20·80	223–24
80	*o*-Anisyl-	*iso*-Propyl-	$C_{18}H_{26}N_6Cl_2O$	259–60	20·32	19·94	165–66
81	*p*-Anisyl-	*iso*-Propyl-	$C_{18}H_{26}N_6Cl_2O$	243–44	20·32	20·04	197–98
82	*p*-Anisyl-	*n*-Butyl-	$C_{19}H_{28}N_6Cl_2O$	241–42	19·67	19·47	183–84
83	*iso*-Propyl-	*iso*-Propyl-	$C_{14}H_{26}N_6Cl_2$	292–93	24·00	23·76	..

The mixture was refluxed for about 20 minutes, the contents cooled in an ice bath, the solid collected, washed with more cold acetone and dried (yield, 17·5 g.). On crystallisation from alcohol, it had m.p. 214–17°.

The same compound was prepared by the action of N-(*p*-chlorophenyl)-N′-*p*-amino-phenylthiourea on isoprophyl isothiocyanate in acetone.

The Di-S-methyl derivatives of the dithiourea derivatives

These were prepared by allowing two molecular equivalents of methyl iodide to react in alcoholic solution with the dithiourea derivatives of formula (VII) listed in Table II. The mixture was shaken and gently refluxed for about 10 minutes and then cooled. The solution was diluted with ether, whereby an oil separated which solidified. The solid was collected.

The majority of the compounds prepared were susceptible to action by light and turned dark. Only a few numbers could be crystallised from alcohol. On heating with higher boiling solvents or even in contact with cold alkalies, these di-S-methyl derivatives suffered decomposition. The compounds prepared are listed in Table III.

Preparation of the diguanidine derivatives of formula (I)

The abovementioned hydriodides of the S-methylisothioureas were dissolved in alcohol, and ammonia gas passed into the boiling solution. After about 20 hours, the reaction mixture was filtered, and concentrated to a small bulk. The free guanidines were liberated by the addition of 20% alkali; the oil that separated was collected, dissolved in ether, dried and mixed with alcoholic hydrochloric acid whereby the hydrochloride separated out as an oil or gum which after separation and trituration with acetone solidified. They were crystallised from acetone and alcohol mixture.

The diguanidines prepared are listed in Table IV.

Action of mercuric oxide and alcoholic ammonia on the dithiourea derivatives.—N-*p*-Chlorophenyl-N′-(*iso*propylthiocarbamido) phenylthiourea (3·79 g.), mercuric oxide (4·7 g.) and alcoholic ammonia (75 c.c. of 18%) were refluxed on the steam-bath for 2 hours. The black mercuric sulphide that was formed was separated and the filtrate after treating with a little charcoal was concentrated to a small bulk. On dilution, a solid was thrown out (1·1 g.). On crystallisation it had m.p. 97–98° (Found: N, 16·30). The analytical figure agrees with that for the diurea compound ($C_{17}H_{19}N_4O_2Cl$) which requires N, 16·15%.

Similarly the action of mercuric oxide and alcoholic ammonia on N-*m*-chlorophenyl-N′-(*p*-isopropylthiocarbamido) phenylthiourea furnished the corresponding diurea derivative, m.p. 115–17° (Found: N, 16·20; $C_{17}H_{19}N_4O_2Cl$ requires N, 16·15%).

N-p-Thiocarbaminophenyl-N′-isopropylthiourea.—*p*-Amino phenyl-isopropylthiourea (10·45 g.) was dissolved in water (120 c.c.) containing con. HCl (4·2 c.c.) and to this was added ammonium thiocyanate (4·2 g.) dissolved in water (15 c.c.). The reaction mixture was concentrated to about a third of its original volume and then cooled in ice-bath. The solid that was thrown out was collected (yield, 9·6 g.) and on crystallisation from alcohol, it had m.p. 200°.

N-p-Aminophenyl-N′-p-chlorophenylguanidine hydriodide (IV).—A mixture of *p*-phenylenediamine (10·8 g.) and S-methyl-*p*-chlorophenylisothiourea

hydriodide (32·8 g.) in alcohol (200 c.c.) was refluxed on the steam-bath for 12 hours, the methylmercaptan that evolved being absorbed in an alkali trap. The solvent was removed from the reaction mixture and the residue stirred with ether whereby the guanidine derivative separated (yield, 24 g.). Crystallised from alcohol, it separated in needles and had m.p. 203° (Found: N, 14·27; $C_{13}H_{14}N_4ClI$ requires N, 14·41%). The picrate had m.p. 206°. The acetyl derivative had m.p. 245–7° (Found: N, 12·90; $C_{15}H_{17}N_4ClI$ requires N, 13·00%).

N-p-Chlorophenyl-N'-p-guanidinophenylthiourea hydriodide (*II*).—A mixture of *p*-aminophenylguanidine hydriodide (11·2 g.), *p*-chlorophenylisothiocyanate (6·67 g.) and acetone (50 c.c.) was refluxed for one hour. The reaction mixture was treated with a little charcoal and filtered. On cooling, the hydriodide of the guanylthiourea separated in fine needles (yield, 5 g.). The mother liquor on dilution with other furnished 2·3 g. more of the compound. On crystallisation from alcohol, it had m.p. 193–94° (Found: N, 15·28; $C_{14}H_{15}N_5SClI$ requires N, 15·64%).

The S-methylisothiourea hydriodide of the above compound was prepared by the action of methyliodide in acetone solution. On crystallisation from acetone, it had m.p. 185–86° (Found: N, 11·74; $C_{15}H_{18}N_5SClI_2$ requires N, 11·55%).

N-p-Chlorophenyl-N'-p-thiocarbamidophenylguanidine (*V*).—To *p*-chlorophenyl-*p*-aminophenylguanidine hydriodide (3·33 g.) dissolved in alcohol (250 c.c.) was added ammonium thiocyanate (0·84 g.) dissolved in water (5 c.c.) and the reaction mixture refluxed for 2 hours on the steam-bath, concentrated to a third of its volume, made slightly alkaline to litmus by addition of 10% sodium hydroxide solution. The reaction product was thrown out as an oil which on keeping solidified (yield, 2·7 g.). This was used as such without purification for the next stage.

The S-methylisothiourea derivative was obtained as an oil and this was also used as such for conversion into the diguanidine derivative.

SUMMARY

Phenylenediguanidine derivatives of formula (I) have been synthesised to assess their antimalarial activity. The method consists in condensing phenylthiourea derivatives of formula (VI) with a series of isothiocyanates, to obtain the dithiourea derivatives (VII), the di-S-methyl derivatives of which reacted with ammonia to furnish the diguanidine derivatives (I). The other methods tried to prepare diguanidine derivatives are also described. Eleven

of the derivatives of formula (I) showed no antimalarial activity when tested against *P. berghi* infections in mice.

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   Schottee *et al.* .. *Z. Physiol. Chem.*, 1928, **174**, 119.

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CHEMOTHERAPY OF MALARIA

Part VIII. Synthesis of Uracils, Thiouracils, Pteridines and Thiopteridines

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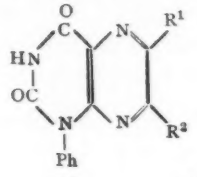
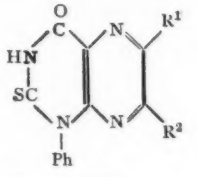
In recent years, the heterocyclic compounds are proving to be fruitful sources of chemotherapeutic agents and of these, derivatives of pyrimidine and pteridine are of special interest. Sulphadiazine and its methyl derivatives are not only potent bacteriostatic agents but show antimalarial properties as well. A number of guanidylpyrimidine derivatives have been discovered by the British workers[1] to show significant antimalarial properties. Recently, outstanding anti-malarial activity has been met with in some 2: 4-diamino-pyrimidines.[2] These point to a need for search for anti-malarials among the pyrimidines. The pteridine derivatives because of their possible interference with folic acid metabolism are also of interest both as bacteriostatic and antimalarial agents. A number of pteridine derivatives have been synthesised and studied[3] by many workers and some have shown antibacterial properties.[4] It has been shown[5] that 2: 4-diamino-6: 7-diphenylpteridine suppresses parasitæmia in chicks infected with *P. gallinaceum*. In view of these, we undertook to synthesise pteridine derivatives of formula (I) and (II), so that these, as well as the intermediate uracil and thiouracil derivatives, could also be tested for their antimalarial as well as their antibacterial properties. The grouping *p*-chlorophenyl and also other substituted phenyl radicals were introduced because this is present in the anti-malarial paludrine.



(I)

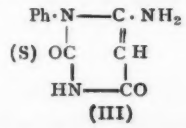
R^1—H, Me, Ph
R^2—H, Me, Ph



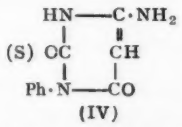
(II)

A number of methods of synthesis of the pteridines have now been examined and of these we have chosen the well-known one consisting of the condensation of the diketones with the 4: 5-diaminouracils and thiouracils, because we are also interested in these intermediates. Suitable phenylurea and phenylthiourea derivatives were condensed with cyanacetic ester according to the method of Traube[6] as improved by Bogert and Davidson.[7] The

reaction proceeded when the reactants were heated in butyl alcohol furnishing the 4-aminouracil and 4-aminothiouracil derivatives respectively. This condensation can lead to two isomers (III) and (IV). Since the condensation of the N-alkyl substituted ureas with cyanacetic ester has been proved to lead to the 3-substituted uracils,[8] we assign the structure (III) to the uracils and thiouracils formed.

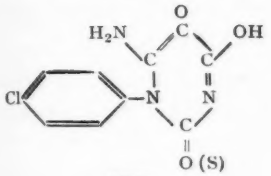


(III)

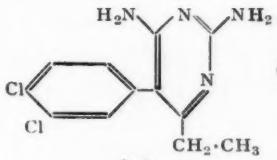


(IV)

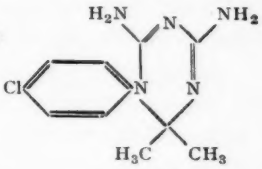
The close formal resemblance between the uracils and thiouracils, and the diaminopyrimidine[2] (V), and the triazine derivative[9] (VI) both of which have been shown to possess outstanding antimalarial activity, as far as the peripheral groups about the ring are concerned, should be noted. Further work done in search of antimalarials of the above type will be reported later on.



(III)

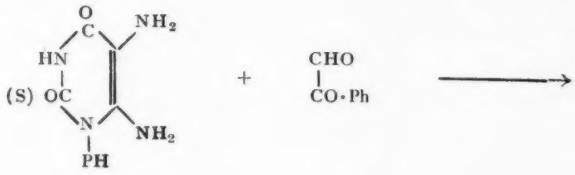


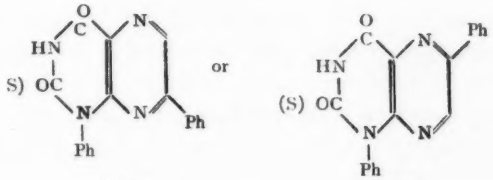
(V)



(VI)

The 4-aminouracils and 4-aminothiouracils were converted into the 4: 5-diamino derivatives through the nitroso derivatives and the pteridines and thiopteridines were prepared by condensing the diamino compounds with glyoxal, diacetyl, phenylglyoxal and benzil individually. In the case of phenylglyoxal, there is the possibility of formation of two isomers (VII) and (VIII).





(VII) (VIII)

On the basis of analogy[10] with previous work, we ascribe the structure (VII) to the compounds obtained. The pteridines and thiopteridines prepared are listed in Tables III and IV.

Of the compounds prepared, a number of representatives are being tested for their antimalarial properties against *P. berghii* infections in mice.

EXPERIMENTAL

Urea and Thiourea Derivatives

Phenyl-, *p*-chlorophenyl-, *m*-chlorophenyl-, *p*-tolyl-, *p*-anisyl-, *o*-anisyl-ureas were prepared by the action of potassium cyanate on the corresponding amine hydrochloride. Phenyl-, *o*-chlorophenyl-, *m*-chlorophenyl-, *p*-chlorophenyl-, *p*-bromophenyl-, *o*-tolyl-, *p*-tolyl-, *o*-anisyl-, and *p*-anisyl- thioureas were prepared by the action of ammonium thiocyanate on the respective amine hydrochlorides.

4-*Aminouracils.*—The compounds listed in Table I were prepared according to the following general method which differs from the standard procedure[6, 7] in the use of butyl alcohol instead of ethyl alcohol.

Sodium (3·5 g.) was dissolved in absolute butanol (125 c.c.), the solution was cooled and to this was added ethyl cyanoacetate (12·5 g.) whereby a bulky white precipitate of the sodium salt separated. After about 30 minutes, *p*-tolylurea (15 g.) was added to this and the mixture gently refluxed for about 30 minutes. The solid went into solution and immediately the condensation product separated. The heating was stopped and the reaction mixture was allowed to stand overnight. Next day it was refluxed for about 30 minutes, the solvent distilled off under reduced pressure, the sodium salt remaining dissolved in water and the uracil obtained by carefully acidifying the clarified solution. The product was separated and washed with water and ether (yield, 16 g.). The product as such could be used in the next stage. A sample was crystallised from dilute alcohol for analysis.

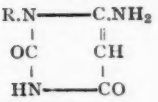
The uracils are soluble in alcohol, acetone, pyridine and dioxane but insoluble in ether and benzene. They dissolve in both dilute hydrochloric acid and alkali.

4-*Aminothiouracils.*—The compounds listed in Table II were prepared essentially as described above, using the thiourea derivatives instead of the urea derivatives.

4: 5-*Diaminouracils and* 4: 5-*Diaminothiouracils.*—The compounds were prepared according to the following method,[7] found to be the best after

TABLE I

4-Aminouracils

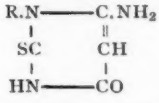


(All the compounds do not melt below 285°)

Serial No.	R	Molecular Formula		Nitrogen % Req.	Found
1	H-	$C_4H_5N_3O_2$		..	..
2	*p*-Chlorophenyl-	$C_{10}H_8N_3O_2Cl$		17·68	17·25
3	*m*-Chlorophenyl-	$C_{10}H_8N_3O_2Cl$		17·68	17·49
4	*p*-Tolyl-	$C_{11}H_{11}N_3O_2$		19·35	19·56
5	*p*-Anisyl-	$C_{11}H_{11}N_3O_3$		18·02	18·16
6	*o*-Anisyl-	$C_{11}H_{11}N_3O_3$		18·02	17·70
7	Phenyl-	$C_{10}H_9N_3O_2$		20·68	20·22
			C %	59·11	59·06
			H %	4·43	4·28

TABLE II

4-Amino-2-thiouracils

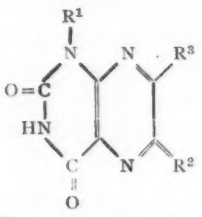


Serial No.	R	Molecular Formula	M.P./°C.		Nitrogen % Req.	Found
1	H-	$C_4H_5N_3OS$	above 295		..	..
2	Phenyl-	$C_{10}H_9N_3OS$	239–240		19·18	19·04
3	*p*-Chlorophenyl-	$C_{10}H_8N_3OSCl$	241–242		16·56	16·37
4	*m*-Chlorophenyl-	$C_{10}H_8N_3OSCl$	218–219		16·56	16·16
5	*o*-Chlorophenyl-	$C_{10}H_8N_3OSCl$	228–229		16·56	16·30
6	*d*-Tolyl-	$C_{11}H_{11}N_3OS$	234–235		18·02	18·32
7	*o*-Tolyl-	$C_{11}H_{11}N_3OS$	226–227		18·02	17·46
8	*o*-Anisyl-	$C_{11}H_{11}N_3O_2S$	222–223		16·86	16·70
9	*p*-Bromophenyl-	$C_{10}H_8N_3OSBr$	242–243		14·09	14·17
10	*p*-Anisyl-	$C_{11}H_{11}N_3O_2S$	212–213		16·86	16·56
				C %	53·01	53·09
				H %	4·41	4·45

many trials. N^3-*p*-Tolyl-4-aminouracil (16·0 g.) was dissolved in a solution of sodium hydroxide (6·4 g. in 160 c.c. water), a solution of sodium nitrite (16·0 g.) in water (80 c.c.) was added, and maintaining at 2 to 5° C., sulphuric acid (100 c.c. of 20 per cent.) was added dropwise under good stirring. The rose-red nitroso compound that separated was collected, filtered, suspended in water (100 c.c.) and made strongly alkaline with ammonia. The nitroso

TABLE III

Pterins



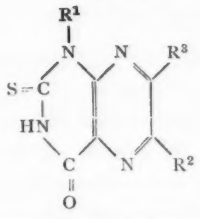
Serial No.	R^1	R^2	R^3	Molecular Formula	M.P./°C.	Nitrogen % Req.	Found
1	H-	CH_3	CH_3	$C_8H_8N_4O_2$	..	..	..
2	Phenyl-	CH_3	CH_3	$C_{14}H_{12}N_4O_2$	above 280	20·89	20·41
3	*p*-Chlorophenyl-	CH_3	CH_3	$C_{14}H_{11}N_4O_2Cl$	above 285	18·51	18·96
4	*m*-Chlorophenyl-	CH_3	CH_3	$C_{14}H_{11}N_4O_2Cl$	above 280	18·51	18·36
5	*p*-Tolyl-	CH_3	CH_3	$C_{15}H_{14}N_4O_2$	above 280	19·85	19·46
6	*p*-Anisyl-	CH_3	CH_3	$C_{15}H_{14}N_4O_3$	289–290	18·79	18·61
7	*o*-Anisyl-	CH_3	CH_3	$C_{15}H_{14}N_4O_3$	257–258	18·79	18·63
						C% 60·40	59·98
						H% 4·69	4·23
8	H-	C_6H_5	C_6H_5	$C_{18}H_{12}N_4O_2$	..	..	..
9	Phenyl-	C_6H_5	C_6H_5	$C_{24}H_{16}N_4O_2$	above 280	14·28	14·58
10	*p*-Chlorophenyl-	C_6H_5	C_6H_5	$C_{24}H_{15}N_4O_2Cl$	above 290	13·13	13·43
11	*m*-Chlorophenyl-	C_6H_5	C_6H_5	$C_{24}H_{15}N_4O_2Cl$	281–282	13·13	13·20
12	*p*-Tolyl-	C_6H_5	C_6H_5	$C_{25}H_{18}N_4O_2$	above 285	13·79	13·74
13	*p*-Anisyl-	C_6H_5	C_6H_5	$C_{25}H_{18}N_4O_3$	above 285	13·27	13·38
14	*o*-Anisyl-	C_6H_5	C_6H_5	$C_{25}H_{18}N_4O_3$	above 290	13·27	12·93
15	*p*-Chlorophenyl-	H	H	$C_{12}H_8N_4O_2Cl$	above 285	20·33	19·99
16	*m*-Chlorophenyl-	H	H	$C_{12}H_8N_4O_2Cl$	242–243	20·33	20·37
17	*p*-Tolyl-	H	H	$C_{13}H_{11}N_4O_2$	above 290	22·04	21·81
18	*o*-Anisyl-	H	H	$C_{13}H_{11}N_4O_3$	276–277	20·74	20·11
19	H-	H	C_6H_5	$C_{12}H_8N_4O_2$	..	..	..
20	Phenyl-	H	C_6H_5	$C_{18}H_{12}N_4O_2$	above 290	17·72	17·88
21	*p*-Chlorophenyl-	H	C_6H_5	$C_{18}H_{11}N_4O_2Cl$	above 295	15·97	15·35
22	*m*-Chlorophenyl-	H	C_6H_5	$C_{18}H_{11}N_4O_2Cl$	above 280	15·97	15·57
23	*p*-Tolyl-	H	C_6H_5	$C_{19}H_{14}N_4O_2$	above 290	16·96	16·73
24	*p*-Anisyl-	H	C_6H_5	$C_{19}H_{14}N_4O_3$	above 295	16·18	16·37
25	*o*-Anisyl-	H	C_6H_5	$C_{19}H_{14}N_4O_3$	above 270	16·18	16·23

compound was filtered, washed well with water. The colour of the nitroso compound in many cases ranged from crimson red to green.

The nitroso compound (13 g.) was suspended in water (100 c.c.) and under efficient mechanical stirring, sodium hydrosulphite (40 g.) was added slowly. While the addition continued, the colour of the product changed

TABLE IV

Thiopterins



Serial No.	R^1	R^2	R^3	Molecular Formula	M.P./°C.	Nitrogen % Req.	Found
1	H-	CH_3	CH_3	$C_8H_8N_4OS$	..	..	..
2	Phenyl-	CH_3	CH_3	$C_{14}H_{12}N_4OS$	280–281	19·71	19·10
3	*p*-Chlorophenyl-	CH_3	CH_3	$C_{14}H_{11}N_4OSCl$	above 270	17·58	17·10
4	*p*-Tolyl-	CH_3	CH_3	$C_{15}H_{14}N_4OS$	above 300	18·79	18·56
5	*p*-Anisyl-	CH_3	CH_3	$C_{15}H_{14}N_4O_2S$	above 280	17·83	17·87
6	*o*-Anisyl-	CH_3	CH_3	$C_{15}H_{14}N_4O_2S$	282–283	17·83	17·53
7	*p*-Bromophenyl-	CH_3	CH_3	$C_{14}H_{11}N_4OSBr$	291–292	15·42	14·92
8	*m*-Chlorophenyl-	CH_3	CH_3	$C_{14}H_{11}N_4OSCl$	266–267	17·58	17·54
					C%	52·74	53·20
					H%	3·45	2·91
9	H-	C_6H_5	C_6H_5	$C_{18}H_{12}N_4OS$	..	..	..
10	Phenyl-	C_6H_5	C_6H_5	$C_{24}H_{16}N_4OS$	274–275	13·72	13·63
11	*p*-Chlorophenyl-	C_6H_5	C_6H_5	$C_{24}H_{15}N_4OSCl$	above 280	12·65	12·84
12	*m*-Chlorophenyl-	C_6H_5	C_6H_5	$C_{24}H_{15}N_4OSCl$	257–258	12·65	12·73
13	*p*-Anisyl-	C_6H_5	C_6H_5	$C_{25}H_{18}N_4O_2S$	297–298	12·78	12·73
14	*o*-Anisyl-	C_6H_5	C_6H_5	$C_{25}H_{18}N_4O_2S$	285–286	12·78	12·68
15	*p*-Bromophenyl-	C_6H_5	C_6H_5	$C_{24}H_{15}N_4OSBr$	above 280	11·49	11·27
16	*p*-Tolyl-	C_6H_5	C_6H_5	$C_{25}H_{18}N_4OS$	above 300	13·27	13·38
					C%	71·09	71·68
					H%	4·26	4·10
17	*m*-Chlorophenyl-	H	H	$C_{12}H_8N_4OSCl$	264–265	19·28	19·44
18	H-	H	C_6H_5	$C_{12}H_8N_4OS$	..	..	..
19	Phenyl-	H	C_6H_5	$C_{18}H_{12}N_4OS$	above 280	16·86	16·41
20	*p*-Chlorophenyl-	H	C_6H_5	$C_{18}H_{11}N_4OSCl$	above 280	15·28	15·39
21	*m*-Chlorophenyl-	H	C_6H_5	$C_{18}H_{11}N_4OSCl$	above 280	15·28	15·36
22	*p*-Tolyl-	H	C_6H_5	$C_{19}H_{14}N_4OS$	above 285	16·18	16·02
23	*p*-Anisyl-	H	C_6H_5	$C_{19}H_{14}N_4O_2S$	above 280	15·46	15·63
24	*o*-Anisyl-	H	C_6H_5	$C_{19}H_{14}N_4O_2S$	above 290	15·46	15·08

from rose red to yellowish white. The mixture was heated on the water-bath for 30 minutes, then cooled and the product that separated collected by filtration, washed with water and finally with alcohol (yield, 10 g.).

The product could not be recrystallised. So it was used as such in the next step. The free bases get oxidised on standing in contact with air.

Pteridines and Thiopteridines

These compounds described in Tables III and IV, were prepared according to the general methods described below:

1-(N^1-*p-Chlorophenyl*)-2: 4-*dioxy*-6: 7-*dimethylpteridine.*—To 3-(N-*p*-chlorophenyl)-4: 5-diaminouracil sulphate (1·6 g.) dissolved in a mixture of glacial acetic acid (30 c.c.) and alcohol (20 c.c.), was added diacetyl (1 c.c.) and the mixture refluxed for 12 hours. The solution was treated with a little charcoal, filtered, the filtrate evaporated to a syrupy mass and diluted with a little water. The product that separated (1·1 g.) was crystallised from a mixture of alcohol and benzene. In 4 per cent. alcoholic alkali the compound showed a bright blue fluorescence in the ultra-violet light.

N^1-(*o-Anisyl*)-2: 4-*dioxy*-6: 7-*diphenylpteridine.*—To 3-(N-*o*-anisyl)-4: 5-diaminouracil sulphate (1·1 g.) dissolved in a mixture of acetic acid (30 c.c.) and alcohol (20 c.c.), benzil (1 g.) was added and the mixture refluxed for about 5 minutes when a solid appeared. Heating was continued for another 8 hours, the mass cooled and filtered. The colourless beautiful needles obtained (yield, 1·1 g.) were separated and recrystallised from a mixture of alcohol and benzene. The alcoholic sodium hydroxide solution of the pteridine showed bright blue fluorescence.

1-(*N-o-Anisyl*)-2: 4-*dioxy*-7-*phenylpteridine.*—To a solution of N^3-*o*-anisyl 4: 5-diaminouracil sulphate (1·1 g.) in 4N acetic acid (50 c.c.) and alcohol (10 c.c.) was added phenylglyoxal hydrate (0·6 g.). Immediately a red solution was obtained and in a few minutes a yellow solid separated. The mixture was refluxed for 30 minutes, the solid was filtered (yield, 1·2 g.) and recrystallised from benzene.

The thiopteridines do not show any fluorescence as also reported by Polonvski.[11]

SUMMARY

Twenty-two pteridines of formula (I) and twenty-one thiopteridines of formula (II) have been synthesised *via* 4-aminouracils and 4: 5-diaminouracils for assessing their antimalarial and antibacterial properties.

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SYNTHETICAL EXPERIMENTS IN THE CHROMONE GROUP

Part XXVIII. Synthesis of 6-Hydroxy-5 : 7-Dimethoxyisoflavone and 5 : 6 : 7-Trihydroxyisoflavone

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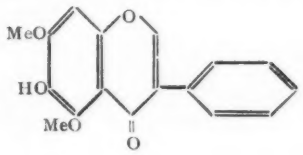
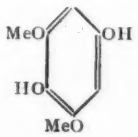
No exceptions to Bose's generalization,[1] that in partially methylated polyhydroxyflavones occurring in nature a methoxyl group is never found in the 5-position, have yet been noticed; but biogenetic considerations do not rule out the occurrence of a hydroxy-5-methoxyflavone. Rao, Rao and Seshadri have shown that isopedicin is 6-hydroxy-5 : 7 : 8-trimethoxyflavanone.[2] Such a type in the isoflavone series is muningin, which King, King and Warwick[3] recently isolated from the heartwood of *Pterocarpus angolensis*, and the constitution of which they proved to be 6 : 4′-dihydroxy-5 : 7-dimethoxyisoflavone. Prunusetin, which Chakravarti and Bhar[4] regarded as 7 : 4′-dihydroxy-5-methoxyisoflavone, has been shown by Narasimhachari and Seshadri[5] to be identical with prunetin, 5 : 4′-dihydroxy-7-methoxyisoflavone. Confirmation of the constitution of muningin by synthesis appears, therefore, to be desirable; this is in progress and, meanwhile, the synthesis of 6-hydroxy-5 : 7-dimethoxyisoflavone (I) is reported.

As stated by Chapman, Perkin and Robinson,[6] 2 : 6-dimethoxyhydroquinone (II), the phenol which would lead to the ketonic intermediates necessary for the synthesis of (I) and its analogues such as muningin, is unreactive in the Hoesch and Friedel-Crafts reactions. By the Fries migration of the diacetate of (II) Mauthner[7] prepared 2 : 5-dihydroxy-4 : 6-dimethoxyacetophenone, but a similar method has not proved to be feasible for the preparation of 2 : 5-dihydroxy-4 : 6-dimethoxyphenyl benzyl ketone

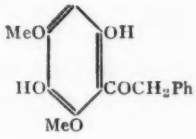


(I)

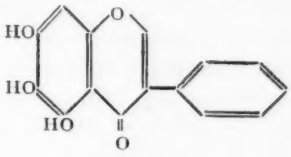


(II)

(III) and other derivatives of phenylacetic acid. The desired ketone (III) has now been prepared by the interaction of the phenol (II) with the boron



(III)



(IV)

trifluoride complex of phenylacetic acid. The action of ethyl orthoformate, pyridine and piperidine[8] on the ketone (III) gave 6-hydroxy-5: 7-dimethoxyisoflavone (I), m.p. 186–87°, in excellent yield. Demethylation with hydriodic acid yielded 5: 6: 7-trihydroxyisoflavone (IV), m.p. 189–90°; this isoflavone analogue of baicalein resembles the latter in exhibiting a characteristic reaction with caustic soda. Baicalein turns deep red with aqueous caustic soda and greenish brown flocks then separate; the isoflavone (IV) first dissolves to form a greenish yellow solution from which a flocculent dark bluish green precipitate separates immediately on shaking.

One of the conditions examined for the preparation of the ketone (III) was to treat the phenol (II) with phenylacetyl chloride dissolved in boron trifluoride-ether complex; the product was the bisphenylacetate of (II).

Experimental

2: 5-*Dihydroxy*-4: 6-*dimethoxyphenyl benzyl ketone* (*III*)

Phenylacetic acid (5 g.) was dissolved in dry chloroform (8 c.c.), and a stream of boron trifluoride was passed into the solution cooled to 10–15°. After the separation of the phenylacetic acid-boron trifluoride complex, 2: 6-dimethoxyhydroquinone (II; 1 g.) was added. The colour of the solution immediately turned yellow. Boron trifluoride was again passed for 15 mins. and the reaction mixture was left overnight at room temperature (25–28°). The clear yellow solution was added to crushed ice and left for two hours. It was then extracted with ether, and the ether-chloroform washed with sodium bicarbonate solution and then with water. The ether-chloroform extract was dried over anhydrous sodium sulphate and the solvents removed by distillation, when a yellow oil (1·75 g.) was obtained. This was distilled twice at 1 mm. and the fraction coming over at 230–50° (air-bath temperature) collected (Found: C, 66·5; H, 5·5. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·5%). The alcoholic solution of the substance gives a dark green colouration with ferric chloride.

6-Hydroxy-5: 7-dimethoxyisoflavone (I)

The ketone (2·5 g.) was dissolved in ethyl orthoformate (3·6 g; 3 mols.) and dry pyridine (20 c.c.). The colour of the solution was yellow. After the addition of piperidine (6 drops) the colour changed to faint brownish yellow. On boiling for 1 hour the colour changed to faint yellow and finally to brownish red. After boiling for 5 hours the solution was cooled, poured over ice and hydrochloric acid and left overnight. The precipitate was collected (2·5 g.), washed and crystallized from alcohol. The colourless needles had m.p. 186–87° (Found: C, 68·4; H, 4·6. $C_{17}H_{14}O_5$ requires C, 68·4; H, 4·7%). The substance gives a bright yellowish green colour with ferric chloride. It dissolves in concentrated sulphuric acid with a very pale yellow colour and in aqueous sodium hydroxide to form a yellow solution. Acetylation in the usual manner by refluxing with acetic anhydride and a drop of pyridine gave the *acetyl* derivative which crystallized from dilute alcohol in colourless needles, m.p. 203–04° (Found: C, 66·8; H, 5·1. $C_{19}H_{16}O_6$ requires C, 67·1; H, 4·7%).

5: 6: 7-Trihydroxyisoflavone (*IV*)

The dimethyl ether (I) (0·5 g.) was heated with acetic acid (1 c.c.), acetic anhydride (1 c.c.) and hydriodic acid (*d.* 1·7; 1 c.c.) at the boil for 4 hours, cooled, diluted with water and treated with sodium bisulphite to destroy free iodine. The precipitate (0·4 g.) was collected, and it crystallized from dilute alcohol in clusters of colourless needles, m.p. 189–90° (Found: C, 66·6; H, 3·6. $C_{15}H_{10}O_5$ requires C, 66·7; H, 3·7%). The substance gives an intense olive green colouration with ferric chloride. It dissolves in concentrated sulphuric acid with a yellow colour. With aqueous sodium hydroxide it forms a greenish yellow solution, and on shaking a flocculent dark bluish green precipitate separates immediately. A dark bluish green flocculent precipitate separates immediately when a drop of sodium hydroxide solution is added to an alcoholic solution of the isoflavone.

The *triacetyl* derivative crystallized from alcohol in colourless needles, m.p. 178° after sintering at 170° (Found: C, 63·4; H, 4·4. $C_{21}H_{16}O_8$ requires C, 63·6; H, 4·0%).

Bisphenylacetate of 2: 6-*dimethoxyhydroquinone*

2: 6-Dimethoxyhydroquinone (0·5 g.; 1 mol.) was mixed with phenylacetyl chloride (1·17 g.; 2 mols.) and boron trifluoride-ether complex (5 c.c.) was added. Phenylacetyl chloride immediately went in solution. The solution was left overnight at room temperature. On pouring into ice, the sticky product was extracted with ether, and the ether extract washed with

aqueous sodium bicarbonate and then with water. The ether solution was dried over anhydrous sodium sulphate and distilled. The sticky residue crystallized from alcohol in colourless needles, m.p. 113° (Found: C, 71·3; H, 5·6. $C_{24}H_{22}O_6$ requires C, 70·9; H, 5·4%).

Summary

In the course of exploratory experiments on the synthesis of muningin 6-hydroxy-5: 7-dimethoxyisoflavone (I) has been synthesized by the action of ethyl orthoformate, pyridine and piperidine on 2: 5-dihydroxy-4: 6-dimethoxyphenyl benzyl ketone (III). The ketone (III) was prepared by the interaction of 2: 6-dimethoxyhydroquinone and the boron trifluoride complex of phenylacetic acid. Demethylation of (I) with hydriodic acid gave 5: 6: 7-trihydroxyisoflavone (IV).

Acknowledgment

Our thanks are due to Dr. T. S. Gore for carrying out the microanalyses recorded in the paper.

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ON THE CHARACTERISTIC METHOD FOR UNSTEADY COMPRESSIBLE FLOW

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Introduction

Gas dynamical problems generally resolve themselves into partial differential equations of the second order. The case of one-dimensional unsteady adiabatic flow of gas when reduced to similar equations is difficult to solve in an exact way except by using Laplace transform. Hilda Geiringer§ has worked out an arithmetical computation for such flow problems using the Lagrangian form of the equation of motion. A graphical computation has been worked out in this paper using the Eulerian equations of motion and continuity based on a method suggested by Prandtl and Busemann.[2] Some reference to earlier work in the field may be found in a paper by R. Saurer.[3] But the method developed in the present paper is more readily applicable than the one given in Saurer's thesis.

The results of the two methods of computation generally agree. But a verification of the result is possible only from data collected from actual engine tests for the case of the diesel cylinder worked out here.

2·0. General Equations of Linear, Unsteady Flow

The one-dimensional, non-steady, adiabatic motion of a compressible fluid is defined by the Euler equation of motion and the equation of continuity:

$$\frac{\partial u}{\partial t} + u \cdot \frac{\partial u}{\partial x} + \frac{1}{\rho} \cdot \frac{\partial p}{\partial x} = 0. \tag{1}$$

and

$$\frac{\partial}{\partial x}(u.\,\rho) + \frac{\partial \rho}{\partial t} = 0 \tag{2}$$

Assuming heat conduction and friction to be negligible, the changes of state in the flow can be taken to be adiabatic. We can then write equation (2) as follows, introducing the velocity potential $u = \frac{\partial \psi}{\partial x}$,

$$\frac{\partial^2 \psi}{\partial x \cdot \partial t} + \frac{\partial \psi}{\partial x} \cdot \frac{\partial^2 \psi}{\partial x^2} + \frac{a^2}{\rho} \cdot \frac{\partial \rho}{\partial x} = 0, \tag{3}$$

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§ Numbers marked within brackets refer to the references cited at the end of the paper.

where a is the velocity of sound, $\sqrt{\frac{\partial p}{\partial \rho}}$.

This leads to the generalised Bernoulli equation:

$$\frac{\partial \psi}{\partial t} + \frac{1}{2}\left(\frac{\partial \psi}{\partial x}\right)^2 = -\int_{\rho_0}^{\rho} a^2/\rho \, d\rho = -f(\rho), \text{ say} \tag{4}$$

Substituting the values of $\frac{\partial \rho}{\partial x}$ and $\frac{\partial \rho}{\partial t}$ in equation (2), we get:

$$-\frac{\rho}{a^2}\left[\frac{\partial^2 \psi}{\partial t^2} + \frac{\partial \psi}{\partial x} \cdot \frac{\partial^2 \psi}{\partial x \cdot \partial t}\right]$$

$$-\frac{\partial \psi}{\partial x}\frac{\rho}{a^2}\left[\frac{\partial^2 \psi}{\partial x \cdot \partial t} + \frac{\partial \psi}{\partial x} \cdot \frac{\partial^2 \psi}{\partial x^2}\right] + \rho \cdot \frac{\partial^2 \psi}{\partial x^2} = 0$$

Multiplying throughout by a^2/ρ and transforming,

$$\frac{\partial^2 \psi}{\partial t^2} + \left[\left(\frac{\partial \psi}{\partial x}\right)^2 - a^2\right]\frac{\partial^2 \psi}{\partial x^2} + 2 \cdot \frac{\partial \psi}{\partial x} \cdot \frac{\partial^2 \psi}{\partial x \cdot \partial t} = 0 \tag{5}$$

This equation does not admit of a general analytical solution which is valid in the whole (t, x) plane. Hence it is necessary to introduce partial solutions which are valid for limited regions. Two such solutions ψ' and ψ'' may be considered, each holding good in a certain region. Representing them as two surfaces situated above the (t, x) plane they cut each other along a curve in space, which is known as the characteristic. Along this characteristic

$$\psi' = \psi'', \ \psi_x' = \psi_x'' \text{ and } \psi_t' = \psi_t''$$

the suffixes indicating the differential.

For the characteristic, the general equation (5) can be written:

$$(\psi_{tt}' - \psi_{tt}'') + 2\psi_x(\psi_{xt}' - \psi_{xt}'') + (\psi_x^2 - a^2)(\psi_{xx}' - \psi_{xx}'') = 0.$$

This is of the form

$$\mathrm{H} \cdot \psi_{xx} + 2\mathrm{K}\psi_{xt} + \mathrm{L}\psi_{tt} + \mathrm{M} = 0$$

An equation of this type has a single solution in a region constituted by a curve and a set of planes tangential to the curve. The region is said to be characteristic if two different solutions are possible in it. For this to be the case, the determinant

$$\begin{vmatrix} \mathrm{H} & 2\mathrm{K} & \mathrm{L} \\ dx & dt & 0 \\ 0 & dx & dt \end{vmatrix} = \mathrm{H} \cdot dt^2 - 2\mathrm{K} \cdot dx \cdot dt + \mathrm{L} \cdot dx^2 = 0$$

that is,

$$dx^2 - 2\psi_x \cdot dx \cdot dt + (\psi_x{}^2 - a^2)\, dt^2 = 0$$

$$[dx - (\psi_x + a)\, dt]\, [dx - (\psi_x - a)\, dt] = 0$$

$$\therefore \quad \frac{dx}{dt} = \psi_x \pm a. \tag{6}$$

This equation gives the projections of the characteristics on the (t, x) plane. But the characteristic cannot be known as the value of ψ_x is not yet determined.

The characteristics form two sets of curves α and β whose tangents have angular coefficients

$$\frac{dx}{dt} = \psi_x + a \text{ and } \frac{dx}{dt} = \psi_x - a$$

Two curves of each set bound a curvilinear quadrilateral in which the solution ψ' is valid. The other solution ψ'' is valid in a neighbouring quadrilateral.

To arrive at an equation which will facilitate numerical computation we have to find next how the partial derivatives ψ_x and ψ_t vary when we pass from one of the quadrilaterals to the next. Now

$$d\psi_x = \psi_{xt} \cdot dt + \psi_{xx} \cdot dx$$

From (6), therefore, it follows

$$\frac{d\psi_x}{dt} = \psi_{xt} + (\psi_x \pm a)\, \psi_{xx}$$

and

$$\frac{d\psi_t}{dt} = \psi_{tt} + (\psi_x \pm a)\, \psi_{xt}$$

Therefore $(\psi_x \mp a)\, \dfrac{d\psi_x}{dt} + \dfrac{d\psi_t}{dt} = (\psi_x{}^2 - a^2)\, \psi_{xx} + 2\psi_x \cdot \psi_{xt} + \psi_{tt} = 0$

or,

$$d\psi_t = -(\psi_x \mp a)\, d\psi_x \tag{7}$$

These are the equations of two sets of curves in the (ψ_t, ψ_x) plane corresponding to the two sets of characteristics mentioned above.

From equation (4),

$$d\psi_t = -\frac{df}{d\rho} \cdot d\rho - \psi_x \cdot d\psi_x .$$

$$d\psi_x \pm \frac{1}{a} \cdot \frac{df}{d\rho} \cdot d\rho = 0$$

$$\psi_x = \mp \int \frac{a}{\rho} \cdot d\rho \tag{8}$$

This is the relation between the density and velocity of the fluid when proceeding along a characteristic. The constant of integration has different values for different characteristics. Assuming an adiabatic flow,

$$a = \sqrt{\frac{dp}{d\rho}} = a_0 \left(\frac{\rho}{\rho_0}\right)^{\frac{k-1}{2}}$$

where a_0 and ρ_0 refer to the conditions at rest. Hence

$$\int \frac{a}{\rho} \cdot d\rho = \frac{2}{k-1} \cdot a$$

Equation (8) can now be put in the form

$$du = \frac{2}{k-1} \cdot da; \quad du = -\frac{2}{k-1} \cdot da \tag{9}$$

or

$$U_2 - U_1 = \mp \frac{2}{k-1} (a_2 - a_1) \tag{10}$$

This equation helps in finding numerically the dependence between the velocity of flow U and the velocity of sound a along a characteristic.

The change in pressure necessary for a change in velocity is obtained from the relation $p_1/p_2 = \left(\frac{a_1}{a_2}\right)^{2k/k-1}$

The graphical approach to the problem of flow now consists in constructing a diagram of position (t, x) and a diagram of state (a, u), Fig. 1. Then suppose we know a and u for two points A and C of the diagram of

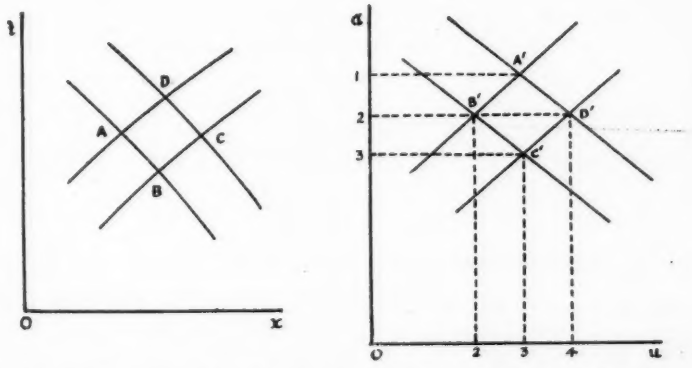

FIG. 1. Relation between the characteristics in the diagram of position (t, x) and the diagram of state (a, u).

position which do not lie on the same characteristic. The points A′ and C′ are then known in the diagram of state and the characteristics passing through them can be drawn, thus fixing B′ and D′. The lines AD and CB are now drawn in the (t, x) plane approximately by a series of consecutive lines inclined at angular coefficients corresponding to a point equidistant between A′D′ and D′C′. The points of intersection of these lines give B and D. Thus the diagram of position can be built up from the boundary conditions.

Equations (6) and (8) can be made non-dimensional by putting

$$A = \frac{a}{a_0} \; ; \; U = \frac{u}{a_0} \; ; \; X = \frac{x}{L} \text{ and } Z = \frac{a_0}{L} \cdot t$$

where L is the reference length. Then

$$\frac{dX}{dZ} = U \pm A \text{ and } dU = \mp \frac{2}{k-1} \cdot dA$$

In this case the A scale may be chosen $2/k - 1$ times the U-scale and the diagram of state then consists of straight lines inclined at 45°. The slope of the diagram of position, Fig. 2 can be obtained with the help of the lines

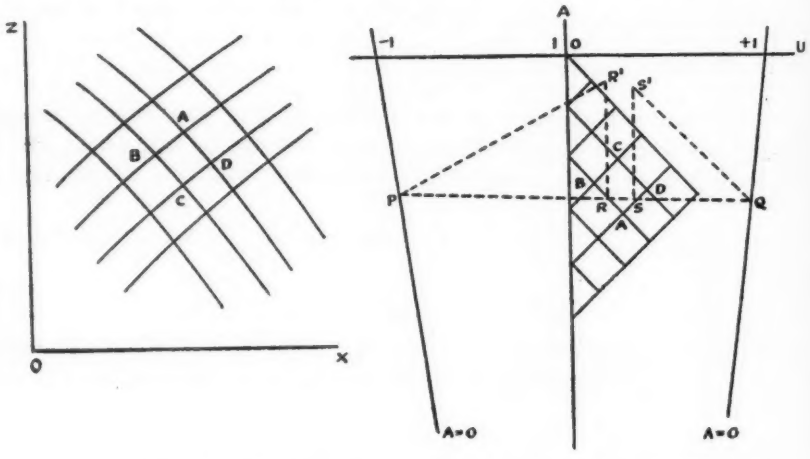

FIG. 2. Method of construction of the Z–X and A–U diagrams by progressive steps.

$U = A$ and $U = -A$. If Z, U and X represent the non-dimensional units, we may draw RR′ and SS′ equal to ZU/X vertically from the points R and S. The lines PR′ and QS′ determine the directions for the diagram of position. In other words the directions AB and AD are parallel to QS′ and PR′.

3.0. Boundary Conditions

Various boundary conditions may now be examined which will refer to problems in internal combustion engines. In general the problem reduces to the flow of gas in a pipe line from an enclosed chamber to the outside. The conditions at the ends of the pipe vary in different cases and can be examined when stating the different boundary conditions.

3.1. We consider the case of a gas flowing from a pressure vessel by the movement of a piston to the atmosphere or into a large vessel through a connecting pipe. The following assumptions are then valid:

1. The layer of gas in the immediate vicinity of the piston has the same velocity as the piston so that the points representing the states of the gas fall on a straight line with the abscissa.
2. The mean pressure in the atmosphere or in the large vessel is constant.
3. The pressure at the outlet cross-section of the pipe is the same as the outside pressure, provided the velocity of gas issuing out of the pipe is not greater than the velocity of sound in the gas. This is only an approximation because the varying quantities of the gas issuing from the pipe cause pressure waves to be propagated in space.

Considering the outlet cross-section as the narrow part of a nozzle, the velocity of sound may not be exceeded. The points of state in the outlet cross-section can in that case be obtained on the horizontal line corresponding to the external pressure p_e and the straight line $A = U$.

The case of the return flow presents an interesting result. The equation for the conservation of energy may be written

$$E_0 = E + \frac{u^2}{2},$$

where E_0 represents the energy content at the state of rest or in the external atmosphere.

But $$E = a^2/k - 1$$

Hence $$a_0^2 = a^2 + \frac{k-1}{2} \cdot u^2$$

a_0 being the velocity of sound in the state of rest. This equation represents an ellipse in the (A, U) diagram and points on this ellipse give the state of the gas at the end of the pipe.

3·2. Let us assume a nozzle at the end of the pipe line. The nozzle outlet conditions are the same as above and we have now to build up the conditions at the nozzle inlet or the outlet end of the pipe with the energy equation and the equation of continuity:

$$a^2 + \frac{k-1}{2} \cdot u^2 = a_1^2 + \frac{k-1}{2} \cdot u_1^2$$

and

$$L\rho u = L_1 \rho_1 u_1$$

or

$$La^{\frac{2}{k-1}} \cdot u = L_1 \cdot a_1^{\frac{2}{k-1}} \cdot u_1,$$

where L is the area of cross-section. Letters without suffixes may be considered referring to the state in the pipe and those with the suffixes to the state in the nozzle outlet. These two equations determine the position of the required states on introducing the values of a and u.

The energy equation can be written

$$A^2 + \frac{k-1}{2} \cdot U^2 = A_1^2 + \frac{k-1}{2} \cdot U_1^2 = A_0^2,$$

where A_0 is the ordinate of the ellipse represented by the above equation. The equation of continuity becomes

$$\left(\frac{A}{A_0}\right)^{\frac{2}{k-1}} \sqrt{1 - \frac{A^2}{A_0^2}} = \frac{L_1}{L} \cdot \left(\frac{A_1}{A_0}\right)^{\frac{2}{k-1}} \sqrt{1 - \frac{A_1^2}{A_0^2}}.$$

This is the equation of all the ellipses and is independent of A_0. We may now draw the family of ellipses with A_0 as parameter.

Now

$$U = \sqrt{\frac{2}{k-1}} \cdot \sqrt{1-A^2}.$$

Hence we may also draw the curves corresponding to

$$f = A^{\frac{2}{k-1}} \sqrt{1-A^2} \text{ and } f_1 = \frac{L_1}{L} \cdot f.$$

The point corresponding to P(A, U) in Fig. 3, namely $P_1(A_1', U_1)$, is obtained directly by drawing the line PQRSTP$_1$. The straight lines QP and TP$_1$ pass through the origin. In this way the desired curve may be drawn from point to point.

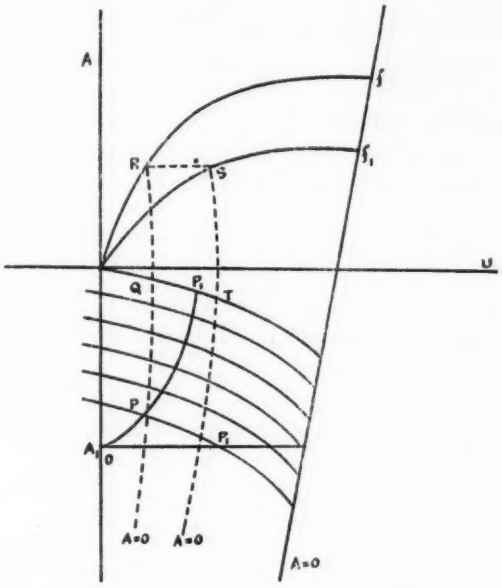

FIG. 3. Diagram of state for a nozzle the curve opp. has to be built from ellipse to ellipse, starting with the conditions at the end of the nozzle.

In the case of the return flow, assuming $u < a$, the nozzle may be regarded as a diffuser. The curve of state is then the left-hand branch of the ellipse with vortex at A.

3.3. We next consider the case of a sudden change in the cross-section of the pipe. This can be reduced to a problem similar to the above by assuming a small nozzle connecting the two sides of the pipe so that the laws of adiabatic flow can still be applied.

Let us distinguish the conditions to the left and the right of the cross-section by the letters l and r, and the states before and after the arrival of the wave from the left and to the right by the suffixes 1 and 2. The three fundamental equations may then be written:

1. Conservation of energy:

$$\frac{k-1}{2} \cdot u_{1l}^2 + a_{1l}^2 = \frac{k-1}{2} \cdot u_{1r}^2 + a_{1r}^2$$

$$\frac{k-1}{2} \cdot u_{2l}^2 + a_{2l}^2 = \frac{k-1}{2} \cdot u_{2r}^2 + a_{2r}^2$$

2. Equation of continuity:

$$L_l \cdot a_{1l}^{\,2/k-1} \cdot u_{1l} = L_r \cdot a_{1r}^{\,2/k-1} \cdot u_{1r}$$

$$L_l \cdot a_{2l}^{\,2/k-1} u_{1l} = L_r \cdot a_{2r}^{\,2/k-1} \cdot u_{2r}$$

3. Characteristics equation:

$$u_{2l} - u_{1l} = -\frac{2}{k-1}(a_{2l} - a_{1l}) \qquad (\alpha)$$

$$u_{2r} - u_{1r} = +\frac{2}{k-1}(a_{2r} - a_{1r}) \qquad (\beta)$$

Of these L_l, L_r, a_{1l}, u_{1l} are known. The system of equations have to be solved for the remaining graphically. Fig. 4 is constructed as before. The

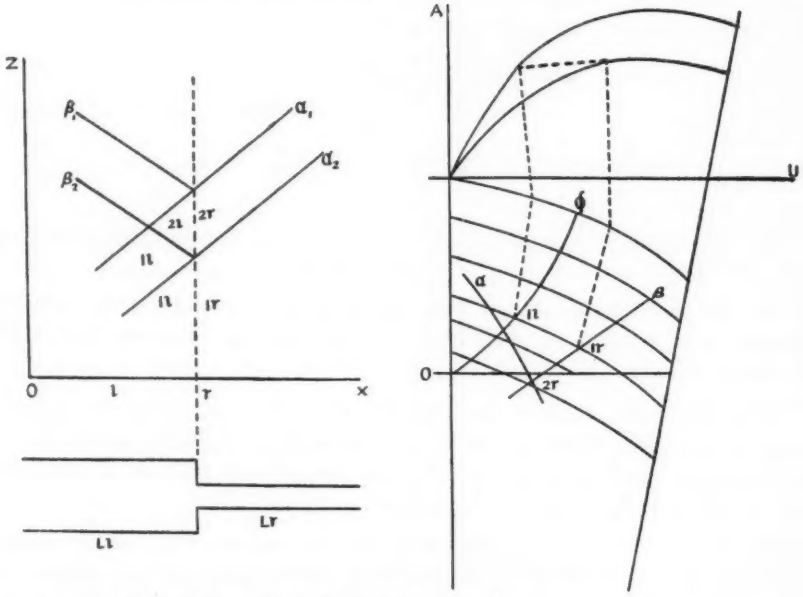

FIG. 4. Diagrams for sudden change of cross-section.

The curve ϕ is obtained as in Fig. 5. $(a_{2l}\ u_{2l})$ is the point of cross-section between ϕ and the characteristic $(a_{1l}\ u_{1l})$. $(a_{2r}\ u_{2r})$ is the intersection between the ellipse through $(a_{2l}\ u_{2l})$ and the characteristic β.

required state (a_{2l}, u_{2l}) is given by the point of intersection of the curve and the characteristics passing through $(a_{1l}\ u_{1l})$. The state $(a_{2r}\ u_{2r})$ is defined by the ellipse passing through $(a_{2l}\ u_{2l})$ and the characteristic passing through $(a_{1r}\ u_{1r})$.

The construction may be repeated in the reverse way for a wave arriving from the right.

3.3.1. It sometimes may happen that the cross-section of the pipe may vary continuously over a certain length. The method described above then becomes difficult to apply. It can be adopted partially to suit such cases where the section changes gradually and where the velocity components at right angles to the axis of the pipe can be neglected.

If the change in the section of the pipe L is $d\mathrm{L}$ over a length dx, then the equation of continuity becomes:

$$\frac{\partial \rho}{\partial t} + \mathrm{U} \cdot \frac{\partial \rho}{\partial x} + \rho \frac{\partial u}{\partial x} + \rho \mathrm{U} \frac{d\mathrm{L}}{\mathrm{L} \cdot dx} = 0$$

Equation (5) then becomes

$$\psi_{tt} + 2\psi_x \cdot \psi_{xt} + (\psi_x{}^2 - a^2)\, \psi_{xx} - a^2 \cdot \psi_x \cdot \frac{d\mathrm{L}}{\mathrm{L} \cdot dx} = 0.$$

The characteristic equations for this case can be written in the form of equation (6) and equation (7). Equation (6) remains:

$$(\psi_x{}^2 - a^2) \cdot dt^2 - 2\psi_x \cdot dx \cdot dt + dx^2 = 0$$

or $$\frac{dx}{dt} = \psi_x \pm a.$$

Equation (7) takes the form

$$(\psi_x{}^2 - a^2)\, d\psi_x + (\psi_x \pm a)\, d\psi_t - a^2 \cdot \psi_x \cdot \frac{1}{\mathrm{L}} \cdot \frac{d\mathrm{L}}{dx} \cdot dx = 0.$$

Substituting for ψ_x and ψ_t, we have

$$du \pm \frac{2}{k-1} \cdot da \pm \frac{au}{u \pm a} \cdot \frac{d\mathrm{L}}{\mathrm{L}} = 0.$$

This equation cannot be integrated and so a diagram of state cannot be constructed independent of the position diagram. The change in the speed of the gas that takes place on the passing of a wave depends on the intensity of the wave as well as the change in the cross-section along the pipe element under consideration.

Introducing $d\mathrm{L} = \frac{d\mathrm{L}}{dx}\, dx$ and $dx = (\mathrm{U} \pm a)$ in the above equation, we have

$$du = \mp \left[\frac{2}{k-1} \cdot da + \frac{1}{\mathrm{L}} \cdot \frac{d\mathrm{L}}{dx} \cdot au \cdot dt \right]$$

or $$da = \mp \frac{k-1}{2} \cdot du - \frac{k-1}{2} \cdot \frac{1}{\mathrm{L}} \cdot \frac{d\mathrm{L}}{dx} \cdot au \cdot dt.$$

In this equation $\frac{1}{\mathrm{L}} \cdot \frac{d\mathrm{L}}{dx}$ is a known function of x and $\frac{1}{\mathrm{L}} \cdot \frac{d\mathrm{L}}{dx} \cdot dt$ can be taken from the diagram of position. The values for (a, u) can be taken from the diagram of state. With these known elements the diagram is constructed as in Fig. 5. We can find two points A_1 and C_1 in the diagram of state corresponding to two given points A and C in the diagram of position.

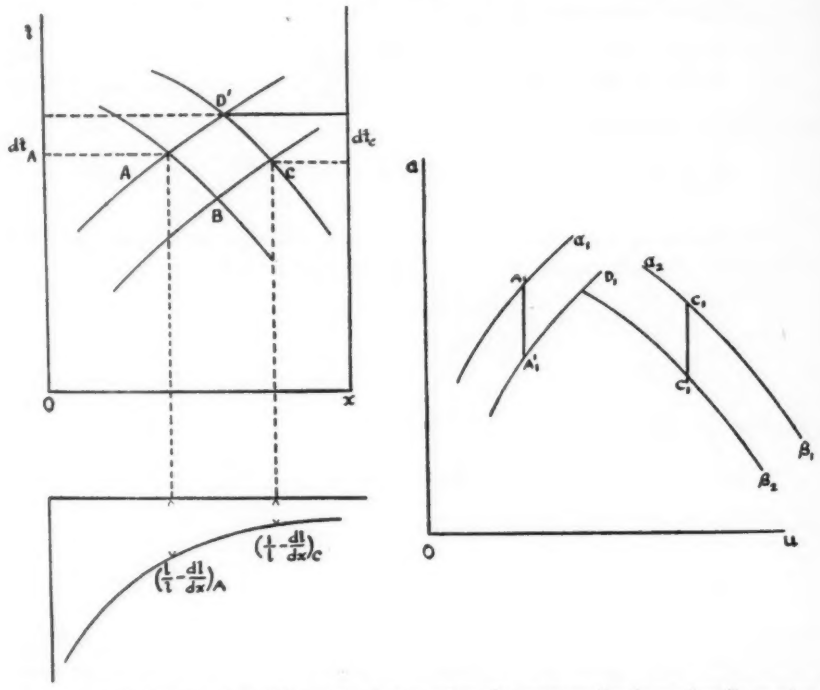

FIG. 5. Diagrams of position and of state when the cross-section is continually varying.

$$A_1 \; A_1' = \frac{k-1}{2} \cdot \frac{1}{l} - \left(\frac{dl}{dx}\right)_A - au \cdot dt_A$$

$$C_1 \; C_1' = \frac{k-1}{2} \cdot \frac{1}{l} - \left(\frac{dl}{dx}\right)_C - au \cdot dt_C$$

1 then remains only to determine the point D_1 in the diagram of state. If D′ be the supposed corresponding point in the diagram of position, we find for dt_A and dt_C the values for $\left(\frac{1}{\mathrm{L}} \cdot \frac{d\mathrm{L}}{dx}\right)_A$ and $\left(\frac{1}{\mathrm{L}} \cdot \frac{d\mathrm{L}}{dx}\right)_C$ plot them equal

to A_1A_1' and C_1C_1'. The point of intersection of the characteristics drawn through A_1' and C_1' is the point D_1. The corresponding point in the diagram of position can then be determined. Ordinarily it is found that D_1 and D' are practically coincident and a second approximation is therefore unnecessary.

3.4. In the three previous cases considered above it has been assumed that the state of the gas at rest is the same throughout the pipe. This is contrary to practice where it generally happens that a quantity of gas at a temperature displaces another quantity of gas at a different temperature. This means that the velocity of sound is not the same along the pipe for the same pressure of the gas. Therefore as the gas moves along the pipe there will be partial reflection of the wave front. We may make an assumption here that there is no diffusion across the zone of separation and that the zone of separation is extremely thin. The zone of separation, it can be seen, moves with the gas with the same velocity as that of the wave front.

Let $(p_{1l}\, a_{1l})$ and $(p_{1r}\, a_{1r})$ represent the pressure and the velocity of sound on either side of the zone of separation initially. A diagram of state $(a_{1l}\, U_{1l})$, $(a_{1r}\, U_{1r})$ can be drawn for each of these regions. The following conditions must obtain at the zone of separation

$$u_{1l} = u_{1r} \text{ and } p_{1l} = p_{1r}$$

If the conditions after the generation of the wave front are represented by $(a_{2l}\, p_{2l}\, u_{2l})$ and $(a_{2r}\, p_{2r}\, u_{2r})$, then

$$p_{2l} = p_{1l}\left(\frac{a_{2l}}{a_{1l}}\right)^{\frac{2k}{k-1}}$$

$$\text{and} \quad p_{2r} = p_{1r}\left(\frac{a_{2r}}{a_{1r}}\right)^{\frac{2k}{k-1}}$$

$$\therefore \quad \frac{a_{2r}}{a_{2l}} = \left(\frac{p_{1l}}{p_{1r}}\right)^{\frac{k-1}{2k}} \cdot \frac{a_{1r}}{a_{1l}}$$

Hence the curves $p_{2l} = \phi(a)$ and $p_{2r} = \phi(a')$ will be identical. The boundary conditions are fulfilled by two points with the same co-ordinates $(a_{2l}\, u_{2l})$ and $(a_{2r}\, u_{2r})$ in the two diagrams. These diagrams can be superposed. If the scale for the $(a_{2l}\, u_{2l})$ diagram is chosen such that the characteristics are inclined at an angle of 45° to the u-axis, then from the above equation the characteristic in the $(a_{2r}\, u_{2r})$ diagram will be inclined at an angle γ given by

$$\tan\gamma = \pm \frac{a_{1l}}{a_{1r}} \cdot \left(\frac{p_{1r}}{p_{1l}}\right)^{\frac{2k}{k-1}}.$$

From this it can be seen that the graphic construction is the same as before. But it is necessary to change the inclination of the characteristics every time the layer of separation is passed through according to the change of state. Thus the partial reflection that occurs when a wave passes through the zone of separation is taken care of. In addition it may be noted that when constructing the diagram the boundary lines $a = \pm u$ drawn for constructing the position diagram also have to be changed.

Fig. 6 shows the graphical construction. The change of temperature from T_1 to T_2 is considered in the diagram. γ_1 and γ_2 give the values for

$$\tan \gamma_1 = \pm \frac{a_{1l}}{a_{1r}} \cdot \left(\frac{p_{1r}}{p_{1l}}\right)^{\frac{k-1}{2k}}$$

and

$$\tan \gamma_2 = \pm \frac{a_{2l}}{a_{2r}} \left(\frac{p_{2r}}{p_{2l}}\right)^{\frac{k-1}{2k}}$$

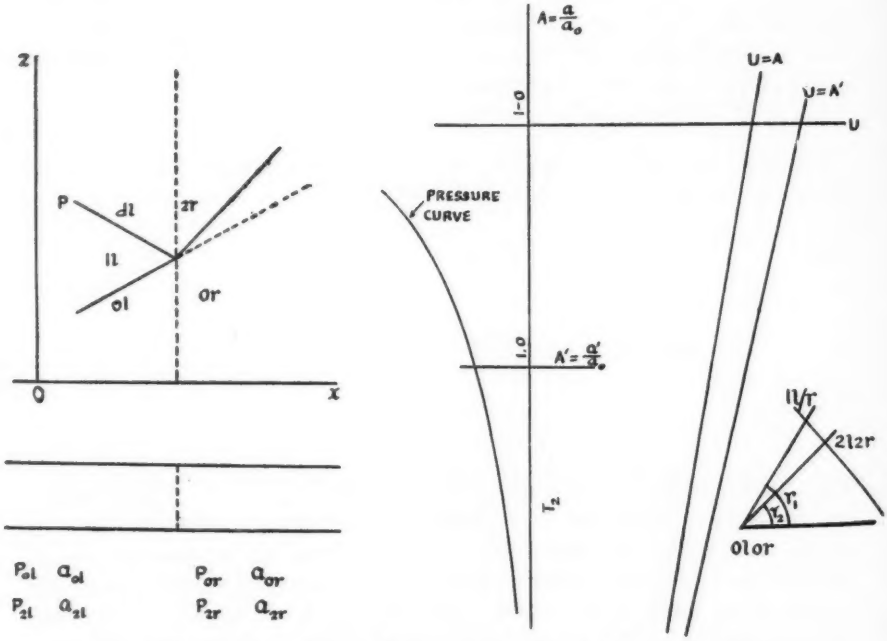

FIG. 6. Diagrams for a change in the temperature of gas flowing in the pipe.

Notice the bounding lines U=A′ and U=A′ are different for the two cases. The a characteristics have to change the inclination.

The change in the slope has to be effected at the zone of separation of the two regions.

4.0. Solution to a Specific Problem

A problem of direct application in internal combustion engines is now examined. Let us consider a diesel engine cylinder of given volume at the time when the gas begins to pass out through the exhaust valve. The movement of the exhaust valve is governed by a known equation. Let the pipe connected at one end to the exhaust valve have a nozzle at the other end. The initial conditions in the cylinder are ($p_0\ a_0$) and in the pipe ($p_0'\ a_0'$), where p_0' is the atmospheric pressure.

Expansion in the cylinder may be considered adiabatic or the curve from an indicator diagram may be used. The relation between the pressures in the cylinder and in the pipe should be such that the velocity of gas through the valve at the beginning of expansion should be equal to the velocity of sound. This will give the condition to be introduced for velocity in the calculation. This is of course contrary to actual practice where it is known that the gas issues through the valve ports at velocities greater than that of sound. This change occurs in actual fact by a shock and not adiabatically. The state of the gas at the entrance to the pipe is determined by this change and is calculated as follows:

$$\mathrm{L}\rho u = \mathrm{L}_1\rho_1 u_1 = \mathrm{L}_1\rho_0 a_0 \left(\frac{2}{k+1}\right)^{\frac{k+1}{2(k-1)}}$$

$$a_0^2 - a^2 = \frac{k-1}{2} \cdot u^2$$

$$a_0^2 - a_1^2 = \frac{k-1}{2} \cdot u_1^2$$

$$u_1^2 = a_1^2 = \frac{2}{k+1} \cdot a_0^2$$

$$\therefore \quad \mathrm{L}p_0' \cdot \frac{u}{u_1} = \mathrm{L}_1 p_0 \left(\frac{2}{k+1}\right)^{\frac{k+1}{2(k-1)}} \left[1 - \frac{k-1}{2} \cdot \frac{u^2}{a_0^2}\right]$$

Knowing the conditions in the cylinder the velocity of flow can now be calculated. Lastly we may consider the characteristic equation:

$$u = u' = \pm \frac{2}{k-1}(a - a')$$

$$= \frac{2}{k-1} \cdot a_0' \left[\left(\frac{p}{p_0'}\right)^{\frac{k-1}{2}} - \left(\frac{p'}{p_0'}\right)^{\frac{k-1}{2}}\right]$$

where (a, p) and $(a_1' p')$ refer to conditions in the cylinder and in the pipe after the shock.

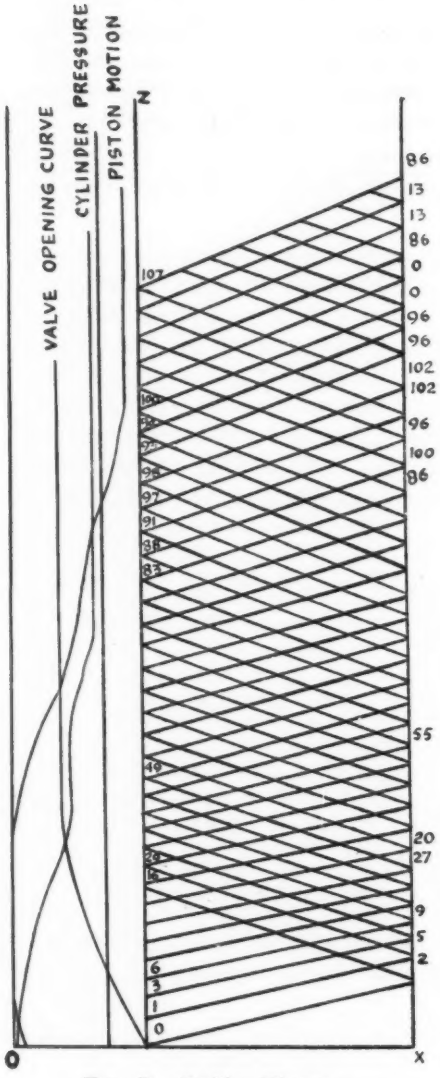

FIG. 7*a*. Position Diagram.

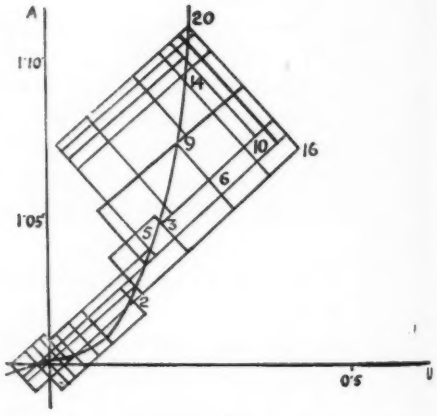

FIG. 7*b*. Diagram of state. Diagrams are for a 1200 RPM. 3·5″×3·75 diesel cylinder.

The original assumption that the velocity with which the gas initially issues out of the cylinder through the valve section is equal to the velocity of

sound leads to the result that the quantity of gas flowing out depends only on the opening and on the pressure in the cylinder and hence is a known function of time. The initial value a_0' in the pipe is naturally varying along the length of the pipe line. But a mean value may be assumed for purposes of calculation.

The terms characterise a known state at any point of the characteristic which cuts the line $X = 0$ at the time Z corresponding to the opening L_1 of the valve. The system therefore reduces to two equations with two unknowns which give the boundary condition at $X = 0$. Figs. 7*a* and 7*b* give the diagrams of position and of state for the pressure waves in the exhaust pipe. With the help of these, Figs. 8*a* and 8*b* can be constructed

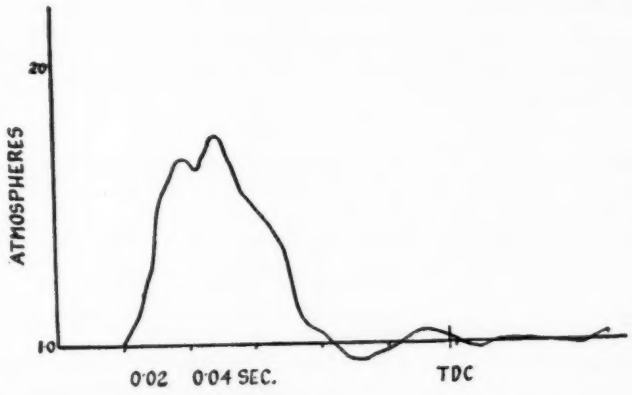

FIG. 8*a*. Pressure at the biginning of the pipe near the valve in the cylinder.

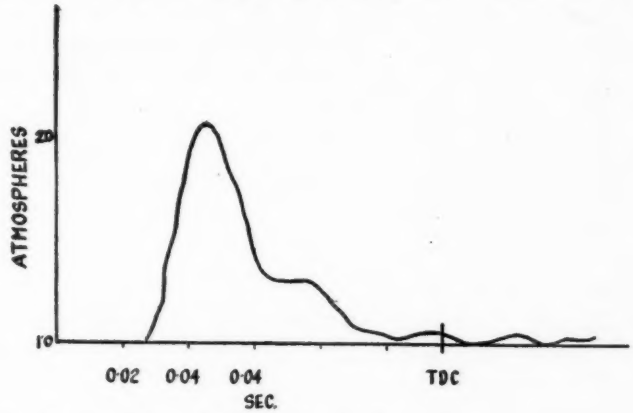

FIG. 8*b*. Pressure at the end of the pipe or at the nozzle.

to give the pressure near the cylinder and the pressure at the end of the nozzle respectively.

CONCLUSION

The method of graphical computation based on the use of characteristics is easier to handle than the arithmetical computation for the study of unsteady flow problems. The possibility of reducing the equations for the characteristics into simple non-dimensional form gives the construction an accuracy comparable with the numerical computation. Regarding the results obtained by this method, it is necessary to verify by actual measurements on pipe flows and engine trials the validity of the simple assumptions made in the graphical computation. The success of the method indicates that it may be possible to use this procedure for the case of the parallel supersonic jet also. In fact the method of characteristics has been successfully employed in the design of a parallel flow jet in some recent work by R. Saurer[5] and K. Foetsch.[6]

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NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

Part XLIV. New Synthesis of Polyhydroxy Coumarins and A Note on Trimethyl Dihydro-Psoralene

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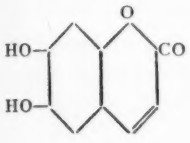
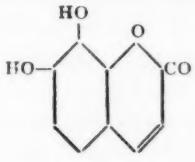
Of the dihydroxy coumarins containing the hydroxyl groups in the benzene ring only three of the six possible arrangements have been known to occur in nature. These are æsculetin (I; 6:7-dihydroxy coumarin), daphnetin (II; 7:8-dihydroxy coumarin) and limettin (III; 5:7-dimethoxy coumarin).



(I)



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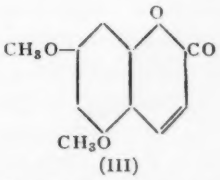
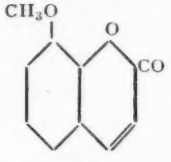


(III)

The other three arrangements, *viz.*, 5:6-, 5:8- and 6:8-, are not so far known to occur in nature. Of these only one has been synthetically prepared earlier, namely, the 6:8-dihydroxy (methoxy) type, by Mauthner[1] who subjected 8-methoxy coumarin (IV) to Elb's persulphate oxidation thus obtaining 8-methoxy-6-hydroxy coumarin (V *a*) which was methylated to give 6:8-dimethoxy coumarin (V *b*).



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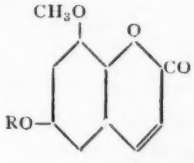


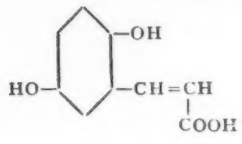
(V)

(*a*) R = H
(*b*) R = CH_3

The other two types, *viz.*, 5:6- and 5:8-dihydroxy coumarins are of interest in connection with the possible occurrence of ring isomerisation, a phenomenon which has been met with in the flavone series. The former has not so far been synthesised. The preparation of the 5:6-dihydroxy coumarins was done in this laboratory during 1950.[2] About the same time

this problem has been studied by Dalvi, Desai and Sethna.[3] They started with 5-methoxy-4-methyl coumarin and subjected it to persulphate oxidation obtaining 6-hydroxy-5-methoxy coumarin which was finally demethylated to give 5: 6-dihydroxy-4-methyl coumarin. Our method of synthesis employs the two stage process of nuclear oxidation and the more readily available 6-hydroxy coumarin (VI *a*) as the starting material. This is made from coumarin itself by persulphate oxidation, a reaction which had already been carried out by Bargellini and Monti.[4] It is now found to be more advantageous to convert coumarin into coumaric acid and subject the latter to persulphate oxidation. The 5-hydroxy coumaric acid (VII) thus obtained is converted into 6-hydroxy coumarin by the action of mercuric chloride. This method follows closely the procedure adopted by Sawhney, Seshadri and Thiruvengadam[5] for the oxidation of 7-methoxy and 7: 8-dimethoxy coumarins. The process can be made continuous giving finally 6-hydroxy coumarin.

6-Hydroxy coumarin undergoes condensation with hexamine to yield the 5-aldehyde (VIII *a*) as a yellow crystalline solid closely resembling in its properties umbelliferone-8-aldehyde.[6] The hydroxy coumarin aldehyde (VIII *a*) undergoes smooth oxidation with alkaline hydrogen peroxide (Dakin's reaction) to yield 5: 6-dihydroxy coumarin (IX *a*). The new dihydroxy coumarin resembles daphnetin (II) and æsculetin (I), dissolving in alkali to give a deep yellow solution and giving a grass green colour with ferric chloride in alcoholic solution. Its dimethyl ether has also been prepared. The dihydroxy compound as well as the dimethyl ether are definitely different from æsculetin and its dimethyl ether.



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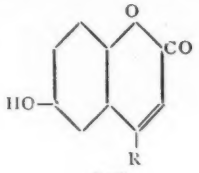

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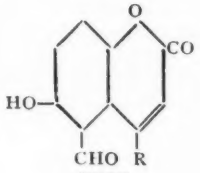
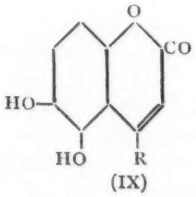
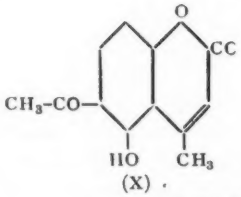


(VIII)



(IX)



(X)

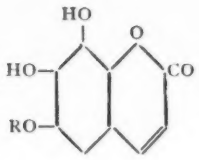
(*a*) R = H
(*b*) R = CH_3

The synthesis of 5: 6-dihydroxy-4-methyl coumarin (IX *b*) has also been effected following a parallel procedure. The starting material 6-hydroxy-4-methyl coumarin (VI *b*) is however made by the condensation of hydroquinone with ethyl acetoacetate in the presence of concentrated sulphuric acid.[7] This method is found to be more convenient than the alternative method involving the persulphate oxidation of 4-methyl coumarin. 5: 6-dihydroxy-4-methyl coumarin (IX *b*) obtained from the corresponding aldehyde (VIII *b*) by this procedure agrees with the description given by Dalvi *et al.*[3] It is definitely different from 4-methyl æsculetin.

Special attention may be drawn here to the activating effect of the 6-hydroxyl group preferentially on the 5-position and not on the 7-position. Similar behaviour has been noticed in the case of the 7-hydroxyl which preferentially activates the 8-position. These observations are explicable on the basis of the tendency of the aromatic double bond to get fixed between 5: 6- and 7: 8-positions. This seems to be a general characteristic of all the benzopyrone (α as well as γ) derivatives.

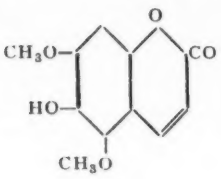
The above aldehyde method of synthesis though much better than the other one involving nuclear oxidation of 5-methoxy-4-methyl coumarin, suffers from the disability that the yield of the aldehyde is poor. A simpler method of obtaining 5: 6-dihydroxy-4-methyl coumarin (IX *b*) is to start with resacetophenone and convert it into 6-acetyl-5-hydroxy-4-methyl coumarin (X) by the method of Sethna, Shah and Shah.[8] This hydroxy coumarin ketone undergoes oxidation with alkaline hydrogen peroxide yielding 5: 6-dihydroxy-4-methyl coumarin (IX *b*).

Of the four possible isomeric trihydroxy coumarins containing the hydroxyl groups in the benzene ring the most commonly occurring in nature is the 6: 7: 8-arrangement of hydroxyl groups. Fraxetin (XI *a*) and its partial methyl ethers fraxidin and isofraxidin belong to this category. The 5: 6: 7-trihydroxy type is met with in fraxinol (XII), and pimpinellin (XIII), a furanocoumarin, may also be considered to be a compound of this type. To the 5: 7: 8-trihydroxy type would belong furanocoumarins like isopimpinellin (XIV), no simpler compound being known. The earlier synthesis of these trihydroxy coumarins followed difficult steps. Recently 6: 7: 8-trihydroxy coumarin (XI *b*) could be obtained more easily from daphnetin dimethyl ether by alkaline persulphate oxidation and subsequent demethylation.[5] Adopting a similar procedure fraxinol (XII) has also been prepared and has been demethylated to 5: 6: 7-trihydroxy coumarin. But the yields in these methods of preparation are poor.[5]



(XI)

(*a*) R = CH_3
(*b*) R = H



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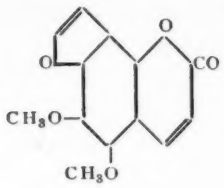
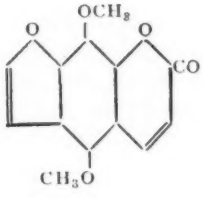


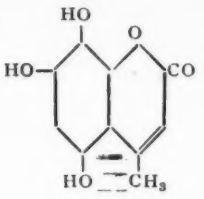
(XIII)



(XIV)

The synthesis of 5:7:8-trihydroxy coumarin and its derivatives does not appear to have been carried out so far. In connection with the study of ring isomerisation in the coumarin series we needed samples of these compounds and have therefore explored convenient methods of their synthesis. 5:7:8-Trihydroxy-4-methyl coumarin (XV) could be prepared from 2:5-dimethoxy resorcinol (XVI)[9] by condensation with acetoacetic ester and subsequent demethylation. The aldehyde (XVII) of this resorcinol also undergoes coumarin condensation with malonic ester. Both these methods work satisfactorily. The aldehyde (XVII) was prepared earlier by Clarke and Robertson[10] using 2:5-dimethoxy resorcinol (XVI) and Gattermann reaction. Recently it has been more conveniently obtained by utilising an earlier intermediate, namely, the dibenzyl derivative of the resorcinol (XVIII)[11] for this purpose and this method has been adopted in the present work. The feasibility of using the dibenzyl derivative directly for the synthesis was first shown by Rao *et al.*,[12] who made from it ω:3:6-trimethoxy-2:4-dihydroxy acetophenone. Subsequently this reaction was studied by Sastri and Seshadri[13] who could also prepare by suitable modifications the 4-benzyl ether of the above ketone. The preparation of the aldehyde (XVII) itself from this dibenzyl ether was described by Sastri in his thesis.[14]

An easier method would be to carry out Dakin's oxidation of 5:7-dihydroxy-8-acetyl-4-methyl coumarin (XIX). In attempting to prepare this ketone it was noticed that Shah and Shah[15] had earlier reported the condensation of phloracetophenone with ethyl acetoacetate in the presence



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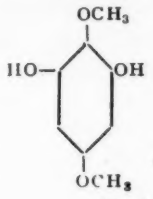

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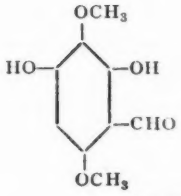

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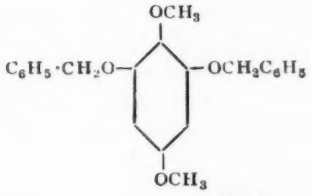
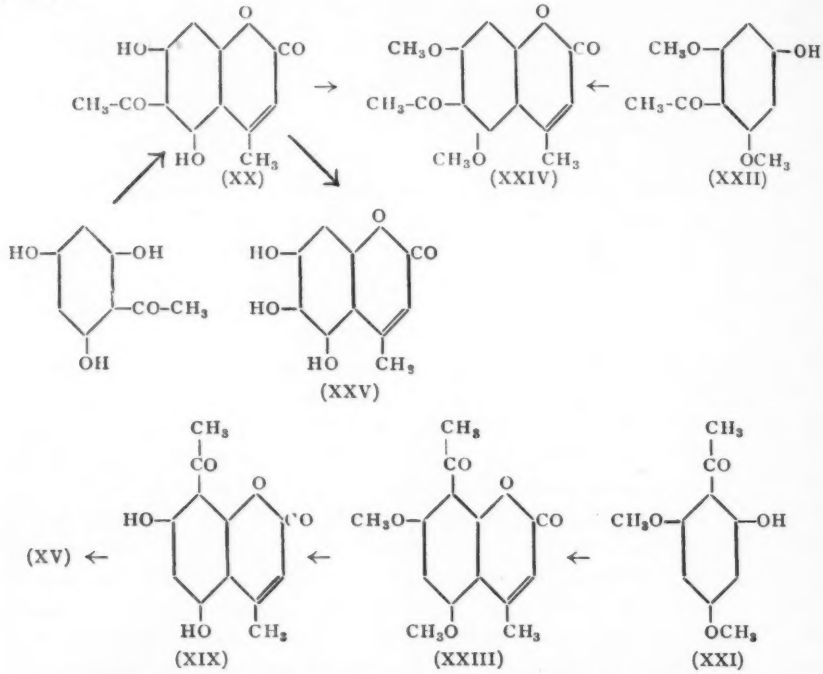


(XVIII)

of concentrated sulphuric acid or anhydrous aluminium chloride. Of the two possibilities for its constitution they felt that it was more likely to be 5: 7-dihydroxy-8-acetyl-4-methyl coumarin (XIX) since it could be readily and completely methylated by methyl iodide in acetone solution in the presence of anhydrous potassium carbonate. This would mean that it is the 2-hydroxyl group of phloracetophenone that takes part in the condensation. But from reactions involving benzoylation,[17a] methylation and benzylation[16] it is known that the 4-hydroxyl group of phloracetophenone is the more reactive one and hence the constitution 5: 7-dihydroxy-6-acetyl-4-methyl coumarin (XX) is more likely to represent the nature of the product obtained by Shah and Shah.[15] In order to settle this issue there was need for unambiguous synthesis of one or both the isomers. For this purpose the two isomeric phloracetophenone dimethyl ethers namely, (i) 2-hydroxy-4: 6-dimethoxy acetophenone (XXI)[17] and (ii) 4-hydroxy-2 : 6-dimethoxy acetophenone (XXII)[17a] are prepared. Each is condensed with ethyl acetoacetate in the presence of concentrated sulphuric acid. The former yields 5: 7-dimethoxy-8-acetyl-4-methyl coumarin (XXIII) which on demethylation with anhydrous aluminium chloride in boiling benzene solution (hydriodic acid could not be used since it produces ununderstandable decomposition of the methoxy ketone) gives rise to 5: 7-dihydroxy-8-acetyl-4-methyl coumarin (XIX) melting at 304–6°. This is different from the compound obtained by the method of Shah and Shah.[15] On the other hand the alternative 2: 6-dimethyl ether of phloracetophenone (XXII) gives rise to 5: 7-dimethoxy-6-acetyl-4-methylcoumarin (XXIV) which is identical with the product obtained by the complete methylation of the dihydroxy ketone

prepared according to the method of Shah and Shah.[15] It is thus clear that the direct condensation of phloracetophenone with ethyl acetoacetate yields only 5:7-dihydroxy-6-acetyl-4-methyl coumarin (XX) and not its isomer (XIX).



The two isomeric dihydroxy coumarin ketones (XIX) and (XX) undergo smooth oxidation with alkaline hydrogen peroxide to yield the two isomeric trihydroxy coumarins, *viz.*, 5:7:8-trihydroxy-4-methyl coumarin (XV) and 5:6:7-trihydroxy-4-methyl coumarin (XXV). They exhibit characteristic difference in their reactions; the former gives with aqueous alkali and sodium carbonate a deep orange colour fading rapidly and finally changing to yellowish green and with ferric chloride a transient green colour changing rapidly to red and also a positive test with *p*-benzoquinone, whereas the latter gives a bright yellow colour with aqueous alkali and sodium carbonate which slowly changes to yellowish green on standing, a blue colour slowly changing to olive brown with ferric chloride and no reaction with *p*-benzoquinone. Thus the production of the trihydroxy coumarins could also be used for establishing the constitution of the corresponding dihydroxy coumarin ketones.

Another point that should be mentioned here is the absence of isomeric change when the dimethyl and trimethyl ethers of 5:7:8-trihydroxy-4-methyl coumarin (XV) are subjected to demethylation with hydriodic acid. The product has all the properties of the 5:7:8-arrangement of hydroxyl groups and is identical with the one obtained by the Dakin's reaction. Even the reverse isomeric change does not occur since the demethylation with hydriodic acid[5] of 4-methyl fraxinol yields a product identical with 5:6:7-trihydroxy-4-methyl coumarin (XXV) obtained independently by the Dakin's method. It is therefore clear that the α-pyrone ring is stable in the presence of hot acids and does not undergo the isomeric change. Ring opening will certainly occur in the presence of excess of alkali but the isomerisation in alkaline conditions could not be studied since the compounds are unstable under these conditions as is evident from the rapid colour change they suffer in alkaline solutions.

Experimental

6-*Hydroxy coumarin* (*VI a*)

Persulphate oxidation through coumaric acid.—Coumarin (12 g.) was dissolved in aqueous sodium hydroxide (12 g. in 15 c.c. of water) yellow mercuric oxide (1·5 g.) was added and the solution shaken vigorously with cooling till all the coumarin dissolved. The solution was filtered and to the resulting filtrate (greenish-yellow fluorescence) sodium hydroxide solution (8 g. in 40 c.c. of water) was added. A saturated solution of potassium persulphate (8 g. in 140 c.c. of water) was added to the above solution cooled in ice-water, with vigorous stirring during the course of 3 hours. After the addition was complete the solution was left overnight and then neutralised with hydrochloric acid (congo red) whereby the unchanged coumaric acid was precipitated. It was filtered off and the filtrate extracted twice with ether to remove any traces of unchanged coumaric acid present. Concentrated hydrochloric acid (100 c.c.) was added to the solution followed by sodium bisulphite (1·5 g.) and it was heated in a boiling water-bath for half an hour. It was then cooled and extracted repeatedly with ether. The dark-brown residue of 4-hydroxy coumaric acid obtained on distilling the ether (3 g.) was dissolved in water (50 c.c.), mercuric chloride (0·5 g.) added and the solution boiled under reflux for an hour. It was then cooled and extracted repeatedly with ether. The ether solution was dried over anhydrous sodium sulphate and the ether distilled off when a pale brown crystalline residue of 6-hydroxy coumarin was obtained. On recrystallisation from alcohol it was obtained as almost colourless needles melting at 248–50°. Yield, 2 g.

6-Hydroxy-coumarin-5-aldehyde (*VIII a*)

A mixture of 6-hydroxy coumarin (3·5 g.), hexamine (7·2 g.) and glacial acetic acid (30 c.c.) was heated for 8 hours in a boiling water-bath, after which a boiling solution of hydrochloric acid (40 c.c. in 40 c.c. of water) was added to it while hot. The solution was left overnight and then distilled under reduced pressure to remove the solvent. The residue was extracted twice with alcohol (20 c.c. each time) and the alcoholic extract concentrated to about 10 c.c. The first two fractions that separated were discarded. 6-Hydroxy coumarin-5-aldehyde could be obtained by concentrating the mother liquor (Yield, 0·5 g.). It was purified by recrystallisation from alcohol and was obtained as almost colourless clusters of rectangular prisms tapering towards the edges, melting at 212–3°. It dissolved in aqueous sodium hydroxide to give a yellow solution and gave a deep pink colour with ferric chloride (Found: C, 62·9; H, 2·9; $C_{10}H_6O_4$ requires C, 63·2; H, 3·2%).

5: 6-*Dihydroxy coumarin* (*IX a*)

6-Hydroxy-coumarin-5-aldehyde (1 g.) was dissolved in aqueous sodium hydroxide (0·3 g. in 25 c.c. of water) and pyridine (5 c.c.) with cooling. To the solution was added hydrogen peroxide (6 c.c., 6%) dropwise with cooling. After the addition was complete the solution was left aside for 2 hours, then acidified, saturated with sodium chloride and extracted with ether repeatedly. The ether solution was washed successively with dilute hydrochloric acid and water and dried over anhydrous magnesium sulphate. On distilling the ether 5: 6-dihydroxy coumarin was obtained as an yellow solid. When recrystallised from ethyl acetate it separated as clusters of yellow needles melting at 256–8°. Yield, 0·8 g. The recorded melting point of æsculetin (6: 7-dihydroxy coumarin) is 270°. It dissolved in aqueous sodium hydroxide to give a bright yellow solution and gave a grass green colour with ferric chloride in alcoholic solution (Found: C, 60·3; H, 2·9; $C_9H_6O_4$ requires C, 60·7; H, 3·4%).

5: 6-*Dimethoxy coumarin*

5: 6-Dihydroxy coumarin (0·5 g.) was methylated by refluxing in acetone (30 c.c.) with dimethyl sulphate (0·6 c.c.) and anhydrous potassium carbonate (2 g.) for 8 hours. 5: 6-Dimethoxy coumarin thus obtained crystallised from methyl alcohol as long colourless rectangular rods melting at 132–3°. (The melting point of 6: 7-dimethoxy coumarin has been reported to be 144°.) It did not dissolve in cold aqueous alkali and gave no colour with ferric chloride (Found: C, 64·0; H, 4·6; $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9%).

6-Hydroxy-4-methyl coumarin-5-aldehyde (VIII b)

A mixture of 6-hydroxy-4-methyl coumarin (4 g.), hexamine (8 g.) and glacial acetic acid (32 c.c.) was heated in a boiling water-bath for 8 hours, after which a boiling solution of hydrochloric acid (40 c.c. in 40 c.c. of water) was added to it while hot. The solution was left overnight and then distilled under reduced pressure. The residue was extracted with boiling alcohol twice (25 c.c. each time) and the alcoholic solution concentrated. The first two fractions that crystallised out consisted of unchanged 6-hydroxy-4-methyl coumarin. 6-Hydroxy-4-methyl coumarin-5-aldehyde was obtained from the alcoholic mother-liquor by further concentration. It was purified by recrystallisation from alcohol and was obtained as clusters of yellow stout rectangular prisms melting at 202–3°. It gave a deep pink colour with ferric chloride and dissolved in aqueous sodium hydroxide to give an yellow solution. Yield, 0·4 g. (Found: C, 64·3; H, 4·4; $C_{11}H_8O_4$ requires C, 64·7; H, 3·9%).

5: 6-*Dihydroxy-4-methyl coumarin (IX b)*

6-Hydroxy-4-methyl coumarin-5-aldehyde (1 g.) was dissolved in aqueous sodium hydroxide (0·3 g. in 25 c.c. of water) and pyridine (5 c.c.) with cooling. The well-cooled solution was treated with hydrogen peroxide (6·5 c.c., 6%) added dropwise. The solution was worked up as in the case of 5: 6-dihydroxy coumarin. The 5: 6-dihydroxy-4-methyl coumarin which was obtained as an yellow solid on distilling off ether crystallised from ethyl acetate as thin rectangular rods melting at 248–50°. It dissolved in aqueous sodium hydroxide to give a deep yellow solution and gave a grass green colour with ferric chloride in alcoholic solution. It agrees in all its properties with the report of Dalvi *et al.*[3]

5: 6-*Dimethoxy-4-methyl coumarin*

5: 6-Dihydroxy-4-methyl coumarin (0·3 g.) was methylated by refluxing in acetone (25 c.c.) with dimethyl sulphate (0·5 c.c.) and anhydrous potassium carbonate (2 g.) for 8 hours. 5: 6-Dimethoxy-4-methyl coumarin crystallised from alcohol as colourless elongated rectangular prisms melting at 127–8°.[3] (Found: C, 65·9; H, 5·4; $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%.)

5: 6-*Dihydroxy-4-methyl coumarin (IX b) by the Dakin's oxidation of 6-acetyl-5-hydroxy-4-methyl coumarin (X)*

6-Acetyl-5-hydroxy-4-methyl coumarin[8] (2 g.) was dissolved in sodium hydroxide solution (12 c.c., 4%) with cooling and to the ice-cold solution hydrogen peroxide (1·8 c.c., 30%, 2 moles) was added dropwise. A little pyridine was added to keep the solution clear and it was set aside at 0° for

2 hours. It was then acidified with ice-cold hydrochloric acid (1: 1), the solid that was precipitated was filtered and washed with a little ice-cold water. On crystallising twice from ethyl acetate the product was obtained as pale yellow thin rectangular rods melting at 248–9°. It gave a bright green colour with ferric chloride in alcoholic solution and dissolved in sodium hydroxide to give an yellow solution. It was identical in its reactions with 5: 6-dihydroxy-4-methyl coumarin and a mixed melting point with the sample described earlier was undepressed. Yield, 1 g.

5: 6-Diacetoxy-4-methyl coumarin obtained by the acetylation of the dihydroxy compound using acetic anhydride and pyridine crystallised from ethyl acetate as colourless needles and melted at 175–6°.

7-Hydroxy-5: 8-dimethoxy-4-methyl coumarin

To a mixture of 2: 5-dimethoxy resorcinol (1 g.) and ethyl acetoacetate (1 g.), cooled in ice, was added twice the weight of ice-cold concentrated sulphuric acid. After leaving overnight, the mixture was poured on crushed ice and the solid that separated was filtered, washed well with water and crystallised from alcohol. 7-Hydroxy-5: 8-dimethoxy-4-methyl coumarin formed rectangular prisms from alcohol on slow crystallisation and elongated needles when crystallised quickly and melted at 218–9°. It gave no colour with ferric chloride in alcoholic solution. Its solution in concentrated sulphuric acid did not exhibit any fluorescence in daylight. The coumarin dissolved readily in sodium hydroxide but the solution exhibited no fluorescence. Yield, 0·8 g. (Found: C, 60·9; H, 5·3; $C_{12}H_{12}O_5$ requires C, 61·0; H, 5·1%).

5: 7-Dimethoxy-8-acetyl-4-methyl coumarin (XXIII)

To a mixture of phloracetophenone-4: 6-dimethyl ether[13] (2 g.) and ethyl acetoacetate (2 g.) cooled to 0° in ice, ice-cold concentrated sulphuric acid (15 c.c.) was added taking care to see that the temperature does not rise above 5° and the mixture left in an ice-bath for 24 hours. The deep yellow solution was then poured into crushed ice (200 g.) with stirring when a very pale yellow solid separated. It was filtered, washed with cold aqueous sodium hydroxide (5%), hot water, and finally hot dilute alcohol. On crystallising twice from alcohol 5: 7-dimethoxy-8-acetyl-4-methyl coumarin separated as colourless rectangular prisms and rods melting at 178–80°. It gave no colour with ferric chloride in alcoholic solution and was insoluble in aqueous alkali. Yield, 0·4 g. (Found: C, 63·7; H, 5·8; $C_{14}H_{14}O_5$ requires C, 64·1; H, 5·3%).

5: 7-*Dihydroxy*-8-*acetyl*-4-*methyl coumarin* (*XIX*)

A benzene solution (80 c.c.) of 5: 7-dimethoxy-8-acetyl-4-methyl coumarin (2 g.) was refluxed with anhydrous aluminium chloride (5 g.) for 2 hours. The solvent was then distilled off, the residue treated with ice and hydrochloric acid (20 c.c.) and left overnight. The colourless solid that separated was filtered, washed with ice-cold dilute hydrochloric acid and then with water. 5: 7-Dihydroxy-8-acetyl-4-methyl coumarin crystallised from alcohol as colourless tiny prisms and melted at 304–6°. It gave a pink colour with ferric chloride and dissolved readily in aqueous sodium carbonate. Yield, 1·2 g. (Found: C, 61·9; H, 4·7; $C_{12}H_{10}O_5$ requires C, 61·6; H, 4·3%).

5: 7: 8-*Trihydroxy*-4-*methyl coumarin* (*XV*)

(i) *Dakin's oxidation of* 5: 7-*dihydroxy*-8-*acetyl*-4-*methyl coumarin.*—To an ice-cold solution of 5: 7-dihydroxy-8-acetyl-4-methyl coumarin (1 g.) in aqueous sodium hydroxide (9 c.c., 4%, 2 moles) hydrogen peroxide (1 c.c., 30%) was added dropwise and the solution kept clear by the addition of a few drops of pyridine. After 2 hours the deep brownish yellow solution was acidified with ice-cold hydrochloric acid when a pale yellow solid separated. It was filtered, washed with water and dried. On crystallising from ethyl acetate it separated as pale yellow small needles and prisms melting at 273–5°. It gave a very transient green colour changing rapidly to red with ferric chloride. It dissolved in aqueous sodium hydroxide and carbonate to give initially a deep orange colour which faded rapidly and finally changed to a yellowish green. With *p*-benzoquinone in absolute alcoholic solution it gave a red colour.

The acetate obtained by heating with acetic anhydride and pyridine crystallised from ethyl acetate-petrol mixture as colourless rectangular rods melting at 148–9°.

(ii) *Demethylation of* 7-*hydroxy*-5: 8-*dimethoxy*-4-*methyl coumarin.*—7-Hydroxy-5 : 8-dimethoxy-4-methyl coumarin (0·6 g.) was dissolved in acetic anhydride (5 c.c.) and heated with hydriodic acid (8 c.c., d. 1·7) and the mixture refluxed (oil-bath) at 140° for 3 hours. The mixture was then poured into water saturated with sulphur dioxide when the trihydroxy coumarin separated as a pale yellow solid. Yield 0·3 g. It was filtered, washed and crystallised twice from alcohol. It came out as pale yellow small needles and prisms and was identical in all its reactions and properties with the trihydroxy compound described in the previous experiment (mixed m.p. 273–5°) (Found: C, 57·5; H, 4·0; $C_{10}H_8O_5$ requires C, 57·7; H, 3·9%).

(iii) *Demethylation of* 5: 7: 8-*trimethoxy*-4-*methyl coumarin*.—The trimethoxy coumarin described below (0·2 g.) was demethylated in acetic anhydride solution (2 c.c.) with hydriodic acid (5 c.c.) and the product worked up as in the above experiment. On crystallising from alcohol it was obtained as pale yellow tiny prisms and needles melting at 273–5°. It was identical with 5: 7: 8-trihydroxy-4-methyl coumarin and mixed melting point with the two samples described in the experiments (i) and (ii) was undepressed.

5: 7: 8-*Trimethoxy*-4-*methyl coumarin*

(i) 5: 7: 8-Trihydroxy-4-methyl coumarin (0·2 g.) obtained by the Dakin's oxidation was refluxed in acetone solution (50 c.c.) with dimethyl sulphate (0·5 c.c.) and anhydrous potassium carbonate (2 g.) for 6 hours. The trimethyl ether crystallised from alcohol as colourless stout rectangular prisms melting at 173–4°. It gave no colour with ferric chloride and was insoluble in aqueous alkali (Found: C, 62·6; H, 5·8; $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·8%).

(ii) 7-Hydroxy-5: 8-dimethoxy-4-methyl coumarin described earlier (0·2 g.) was methylated with excess dimethyl sulphate as in the above experiment; the trimethyl ether was identical with the product described above (m.p. and mixed melting point 173–4°).

5: 7-*Dimethoxy*-6-*acetyl*-4-*methyl coumarin* (*XXIV*)

(i) *From* 2: 6-*dimethoxy*-4-*hydroxy acetophenone*.—This was prepared by the same method as was used for the corresponding-8-acetyl compound described earlier, starting with 2: 6-dimethoxy-4-hydroxy acetophenone.[17a] The product crystallised from alcohol as fine needles melting at 173–4° and gave no colour with ferric chloride. A mixed melting point with a sample of 5: 7-dimethoxy-8-acetyl-4-methyl coumarin was considerably depressed (140–3°).

(ii) *Methylation of the product* (*XX*) *obtained from phloracetophenone and ethyl acetoacetate*.—The dihydroxy-acetyl-4-methyl coumarin obtained by the method of Shah and Shah[15] was methylated by refluxing it (0·5 g.) in acetone solution (100 c.c.) with dimethyl sulphate (0·5 c.c., excess) and anhydrous potassium carbonate (1·5 g.). The methyl ether was obtained from alcohol as colourless long rectangular prisms and needles melting at 173–5° (Shah and Shah reported the melting point as 165–6°). It was insoluble in cold aqueous sodium hydroxide and gave no colour with ferric chloride. It was identical with 5: 7-dimethoxy-6-acetyl-4-methyl coumarin and a mixed melting point with the synthetic sample described above was

undepressed while that with 5: 7-dimethoxy-8-acetyl-4-methyl coumarin was considerably depressed (143°).

5: 6: 7-*Trihydroxy*-4-*methyl coumarin* (*XXV*)

Dakin's oxidation of 5: 7-*dihydroxy*-6-*acetyl*-4-*methyl coumarin* (*XX*).—5: 7-Dihydroxy-6-acetyl-4-methyl coumarin (1 g.) dissolved in sodium hydroxide solution (4 c.c., 4%, 2 moles) was cooled in ice and treated with hydrogen peroxide (1 c.c., 30%) a little pyridine being added to get a clear solution. The initial yellow colour changed to yellowish-brown. After keeping in an ice-bath for 2 hours the solution was acidified with hydrochloric acid and the solid obtained was filtered and washed with water. After drying it was crystallised from ethyl acetate twice when it separated as pale yellow thin plates melting at 278–80°. (Parikh and Sethna[5] reported the same melting point). Ether extraction of the aqueous solution gave some more of the product. Total yield 0·5 g. 5: 6: 7-Trihydroxy-4-methyl coumarin gave a blue colour changing rapidly to green and finally olive-brown colour with ferric chloride. It dissolved readily in aqueous sodium hydroxide and carbonate to give a bright yellow solution changing to yellowish green. The mixture with 5: 7: 8-trihydroxy-4-methyl coumarin melted at 230°.

The triacetate crystallised from ethyl acetate as colourless mass of woolly needles melting at 159–60°. A mixture with 5: 7: 8-triacetoxy-4-methyl coumarin melted at 130°.

The trimethyl ether obtained by methylation with excess dimethyl sulphate and anhydrous potassium carbonate in acetone solution crystallised from alcohol as colourless rectangular prisms and melted at 115–6°.[5]

7-*Hydroxy*-5: 8-*dimethoxy*-3-*carbethoxy coumarin*

2: 4-Dihydroxy-3: 6-dimethoxy benzaldehyde (0·5 g.) was added to malonic ester (0·5 g.) and then treated with a few drops of piperidine with cooling under the tap. The deep reddish brown mixture was allowed to stand at laboratory temperature for 24 hours and then gently warmed on the water-bath for 10 minutes. Ice-water containing a few c.c. of hydrochloric acid was added, when the carbethoxy-coumarin was precipitated as a crystalline solid. It was collected, washed and recrystallised from alcohol. The 3-carbethoxy-coumarin was obtained as big rectangular plates from alcohol on slow crystallisation and clusters of needles when rapidly crystallised and melted at 230–2°. Yield almost quantitative. It dissolved in aqueous sodium hydroxide to give a deep yellow solution which showed no fluorescence and gave no colour with ferric chloride in alcoholic solution. Its solution in concentrated sulphuric acid exhibited no fluorescence in daylight (Found: C, 57·4; H, 4·7; $C_{14}H_{14}O_7$ requires C, 57·2; H, 4·8%).

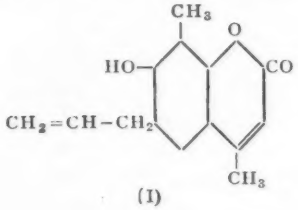
SUMMARY

6-Hydroxy coumarin and 6-hydroxy-4-methyl coumarin are condensed with hexamine to yield the corresponding 5-aldehydes, which undergo Dakin's oxidation smoothly yielding the corresponding 5: 6-dihydroxy coumarins. The 6-hydroxyl group activates predominantly the 5-position. 5: 6-Dihydroxy-4-methyl coumarin is more conveniently prepared by the Dakin's oxidation of the readily available 6-hydroxy-5-acetyl-4-methyl coumarin.

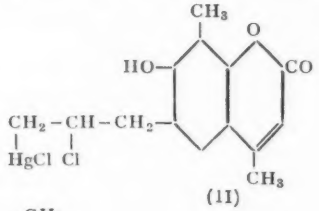
5: 7: 8-Trihydroxy coumarin derivatives are obtained from (1) 2: 5-dimethoxy resorcinol by Pechmann condensation, (2) from the aldehyde of the above resorcinol by malonic ester condensation, and (3) by Dakin's oxidation of 5: 7-dihydroxy-8-acetyl-4-methyl coumarin. The 8-acetyl compound required for this purpose is made from 4: 6-dimethyl phloracetophenone by condensation with ethyl acetoacetate and final demethylation with anhydrous aluminium chloride. It is shown that direct condensation of phloracetophenone with acetoacetic ester yields the isomeric 5: 7-dihydroxy-6-acetyl-4-methyl coumarin which on oxidation yields 5: 6: 7-trihydroxy-4-methyl coumarin. No isomeric change is noticed when the methyl ethers of these trihydroxy coumarins are boiled with hydriodic acid.

A Note on the Synthesis of α: 4: 8-*Trimethyl dihydro-psoralene*

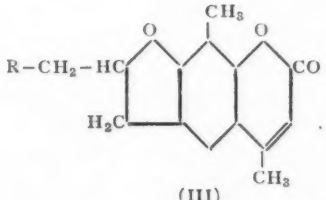
With a view to compare the toxic properties of angular coumarinofuran derivatives with the corresponding linear ones the abovementioned compound has been prepared using the method of Adams *et al.*,[18] with the modifications adopted by Krishnaswamy and Seshadri.[19] Since in many reactions of 7-hydroxy coumarins the 8-position is far more reactive than



(I)



(II)



(III)

(*a*) R = I
(*b*) R = H

the 6-position the former has to be blocked by means of an alkyl group in order to obtain the linear coumarino-furan derivative. 7-Hydroxy-6-allyl-4: 8-dimethyl coumarin (I) had already been reported by Rangaswami and Seshadri.[20] This is treated with mercuric chloride in methyl alcoholic solution; the addition product (II) yields the α-iodomethyl dihydro furan (III *a*) on treatment with a solution of iodine in potassium iodide. When this is reduced by sodium and alcohol α: 4: 8-trimethyl dihydro-psoralene (III *b*) is obtained.

Experimental

7-Hydroxy-4: 8-dimethyl-6-allyl coumarin (I)

The following modification of the original method[20] gave better yields of the pure product. The reaction is carried out at a lower temperature and under reduced pressure.

7-Allyloxy coumarin (1·5 g.) was heated in a test-tube at 195–200° under reduced pressure (water pump) using an oil-bath for 2 hours. After cooling the brown mass was extracted with hot alcohol and filtered hot through animal charcoal. The crystalline solid that separated was again crystallised from dilute alcohol, when 7-hydroxy-6-allyl-4: 8-dimethyl coumarin was obtained in the form of star-like clusters of short needles and rectangular plates melting at 168–9°. Yield 1·2 g. It dissolved in aqueous sodium hydroxide giving blue fluorescence and gave no colour with ferric chloride in alcoholic solution.

Mercuric chloride addition compound (II)

The allyl coumarin (1 g.) dissolved in a slight excess of methyl alcohol, was treated with a clear cold saturated solution of mercuric chloride (1·5 g.) in the same solvent and the clear mixture allowed to stand at the laboratory temperature. It gradually deposited a crystalline solid in about an hour; after 48 hours the colourless addition product was collected, washed well with hot methyl alcohol in which it was sparingly soluble and dried. Yield, 1·75 g. It appeared as elongated rectangular prisms and decomposed at 265° with previous sintering at 245°. It was difficultly soluble in aqueous sodium hydroxide and the alkali when kept in contact with the solid for some time developed a weak blue fluorescence (Found: Cl, 13·9; $C_{14}H_{14}O_3\,HgCl_2$ requires Cl, 14·2%).

4: 8-Dimethyl coumarino-α-iodomethyl dihydro-7: 6-furan (III a)

The mercuric chloride addition product (1·5 g.) was added in small quantities at a time to a fairly concentrated solution of iodine in potassium iodide (20 c.c.) with stirring and heated in the water-bath for an hour. The solid was then collected, washed well with water and a little alcohol. It was

dissolved in excess of alcohol and filtered from a small quantity of unchanged material. The alcoholic filtrate on concentration and allowing to stand, deposited the iodo-compound as a crystalline solid which was collected and recrystallised from alcohol. It was obtained as fine needles melting at 144–5° and was insoluble in aqueous sodium hydroxide. Yield, 1·3 g. (Found: C, 47·1; H, 4·0; $C_{14}H_{13}O_3I$ requires C, 47·2; H, 3·7%).

α: 4: 8-*Trimethyl coumarino-dihydro*-7: 6-*furan* (*III b*)

The α-iodomethyl compound (1 g.) was dissolved in absolute alcohol (40 c.c.) and small pieces of sodium metal (2 g.) were pressed to the bottom of the container by means of a glass rod, the addition of sodium was continued till the reaction became slack. The solution was then diluted with water (100 c.c.) and acidified with concentrated hydrochloric acid, when the α-methyl dihydro furan separated out as a crystalline solid. It was collected, washed with water and recrystallised from alcohol. It was obtained as broad plates tapering at the ends on slow crystallisation and short needles when crystallised quickly, and melted at 230–1°. It was insoluble in hot dilute sodium hydroxide solution and gave no colour with ferric chloride in alcoholic solution. Yield, 0·15 g. (Found: C, 73·1; H, 5·9; $C_{14}H_{14}O_3$ requires C, 73·0 H, 6·1%).

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THE OPTICAL ROTATORY DISPERSION OF CINNABAR

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1. Introduction

Cinnabar is the bright red crystalline form of mercuric sulphide which occurs as hexagonal prisms or plates belonging to the space group D_3^4 (or the enantiomorphous D_3^6). The crystal exhibits a very marked optical rotatory power. This has been measured for a direction coinciding with the optical axis by several workers, notably by Becquerel (1908), Rose (1910) and Molby (1910). At room temperature, measurements have been made only upto the yellow line of sodium, since in these circumstances the crystal is almost completely opaque beyond that wavelength. But at liquid-air temperature, the measurements have been extended farther into the shorter wavelength region, for at such a low temperature, even a specimen as thick as 1·5 mm. transmits light upto 5600 A.U. The values obtained by the different authors do not agree very well, probably due to the variations in the quality of the specimens employed. But even so, it is clear that the rotatory power of cinnabar is extremely large and also that it varies considerably with the wavelength, the value increasing by about four times as we proceed from 7200 to 6000 A.U. Another fact which emerges from the observations of Becquerel and Molby is that the rotation increases notably when the temperature of the crystal is raised. As far as can be judged from the present data, the rate of variation of the rotatory power with temperature increases with decrease of wavelength at a much faster rate than does the rotatory power itself.

In the present paper, it is proposed to consider the variation of the rotatory power with wavelength as also with temperature. It is shown that a Drude equation does not fit the rotatory dispersion satisfactorily, whereas a formula of the type

$$\rho = \frac{k\lambda^2}{(\lambda^2 - \lambda_0^2)^2} \tag{1}$$

represents it much better. By assuming that the characteristic absorption wavelength λ_0 shifts with temperature, it has been possible to quantitatively account for the temperature coefficient of the rotatory power.

2. THE ROTATORY DISPERSION FORMULA

Rose (*loc. cit.*) has attempted to fit his experimental data by means of a rotatory dispersion formula similar to that suggested by Drude for quartz (1900), but with both terms having the same sign. The formula proposed by him is

$$\rho = \frac{21{\cdot}8835}{\lambda^2 - 0{\cdot}31821} + \frac{1{\cdot}6361}{\lambda^2} \tag{2}$$

The first term which accounts for the bulk of the rotation makes use of an absorption at about 5640 A.U., while the second term represents the small contribution due to a characteristic frequency lying in the extreme ultra-violet. The values calculated from this formula are given with the experimental data of Rose in Table I. Throughout ρ is expressed in degrees per millimetre and λ in microns.

TABLE I

λ	$\rho_{(\text{expt.})}$	$\rho_{(\text{calc.})}$	$\rho_{\text{calc.}} - \rho_{\text{expt.}}$
·5983	554·98	554·96	− 0·02
·6022	489·64	497·05	+ 7·41
·6103	417·00	407·77	− 9·23
·6136	396·44	379·65	−16·79
·6192	365·37	339·91	−25·46
·6247	337·42	307·97	−29·45
·6278	322·50	292·40	−30·10
·6337	303·43	266·59	−36·84
·6495	255·60	215·59	−40·57
·6563	241·40	198·29	−43·11
·6870	182·00	145·79	−31·21
·7187	132·57	113·51	−19·06
·7621	86·16	86·16	0·00

It can be seen that the experimental values differ from those calculated in a systematic fashion, the deviation being throughout rather large and negative. Apart from this, there is another objection to the formula proposed, namely, that it assumes the existence of a characteristic absorption wavelength at 5640 A.U., while actually, according to the observations of Becquerel,

cinnabar is capable of transmitting light upto 5600 A.U. at liquid-air temperature, and at that temperature the rotatory power for that wavelength is only about 1·75 times larger than that for 6000 A.U. and of the same sign. These facts indicate *prima facie* that the characteristic absorption band lies farther out towards the blue end of the spectrum, though, of course, both its position and width may be expected to be temperature-sensitive.

In an earlier paper (1953), the present author had given a theoretical interpretation of the optical activity of quartz, in which the expression for the rotatory power had been derived to be of the same general type as (1). We shall see whether the same theory may be applied to the case of cinnabar. The structure of cinnabar is similar to that of quartz, both crystals belonging to the space group D_3^4 or D_3^6. Also, just as for quartz, the optical activity of cinnabar is purely a consequence of its crystal structure. Obviously then, whatever arguments hold good for quartz should be applicable to the case of cinnabar and hence its rotatory power should be capable of being fitted by a similar formula. In fact, the following formula is found to represent it well, as can be seen from Table II.

$$\rho = \frac{19{\cdot}13\,\lambda^2}{(\lambda^2 - 0{\cdot}243)^2} \tag{3}$$

TABLE II

λ	$\rho_{(\text{expt.})}$	$\rho_{(\text{calc.})}$	$\rho_{\text{calc.}} - \rho_{\text{expt.}}$
·5983	555	518	− 37·0
·6022	489·6	484·6	− 5·0
·6103	417·0	425·1	+ 8·1
·6136	396·4	404·0	+ 7·6
·6192	365·4	372·0	+ 6·6
·6247	337·4	344·3	+ 6·9
·6278	322·5	330·1	+ 7·6
·6337	303·4	305·5	+ 2·1
·6495	255·6	255·1	− 0·5
·6563	241·4	233·8	− 7·6
·6870	182·0	172·2	− 9·8
·7187	132·6	132·0	− 0·6
·7621	86·2	97·4	+11·2

The formula makes use of an absorption at 4930 A.U. which is well within the limit of continuous absorption of light and therefore, is certainly more reasonable than the wavelength occurring in (2).

It can be seen that the fit is throughout good except for λ 5983 A.U. and λ 7621 A.U. But even this discrepancy is not of any significance. For, the uncertainty of the measurement of the rotatory power has been found by Rose to be much larger for these two wavelengths than for the others. Also it will be noticed that the difference between the calculated and experimental values is not of a progressive nature, being sometimes positive, sometimes negative.

It can easily be shown that the characteristic wavelength appearing in (3) can also fit the ordinary dispersion curve fairly well. Accordingly, a formula of the Sellmeyer-Drude type involving this wavelength has been fitted up for the ordinary index. It is found that the bulk of the refraction is due to an extreme ultraviolet term whose contribution has been replaced by a constant. The formula is

$$n^2 - 1 = 5{\cdot}7 + \frac{0{\cdot}5594\,\lambda^2}{\lambda^2 - 0{\cdot}243} \qquad (4)$$

The calculated and experimental values are given in Table III. The data were obtained from the *International Critical Tables* (1930).

TABLE III

λ	$n_{(\text{expt.})}$	$n_{(\text{calc.})}$
·599	2·903	2·904
·6075	2·887	2·887
·6239	2·865	2·863
·6439	2·842	2·838
·6720	2·816	2·813
·7077	2·789	2·790
·7621	2·760	2·768

It will be seen that the agreement is tolerably good, thus indicating that the characteristic wavelength at 4930 A.U. approximately represents the actual dispersion wavelength of cinnabar.

3. THE TEMPERATURE VARIATION OF THE ROTATORY POWER

We shall now discuss the influence of temperature on the optical rotatory power. In an earlier paper (1952), the present author had quantitatively

accounted for the temperature coefficient of the rotatory power of quartz over a wide region of the spectrum by assuming that the characteristic frequency shifts with temperature. We shall now apply the same method to the case of cinnabar. As was done for quartz, we shall neglect all considerations of thermal expansion in these calculations as its contribution to the temperature coefficient is comparatively small. The rotatory dispersion formula (1) may be expressed in the form

$$\rho = \frac{a\nu^2}{(\nu_0^2 - \nu^2)^2}, \tag{5}$$

where $\nu = 1/\lambda$ and $k = a\lambda_0^4$. Differentiating with respect to temperature, we get

$$\frac{d\rho}{dt} = \frac{4\,a\nu^2\nu_0^2}{(\nu_0^2 - \nu^2)^3}\chi_0$$

$$= \frac{4\,k\lambda^4}{(\lambda^2 - \lambda_0^2)^3}\chi_0, \tag{6}$$

where $$\chi_0 = -\frac{1}{\nu_0}\frac{d\nu_0}{dt} = \frac{1}{\lambda_0}\frac{d\lambda_0}{dt}.$$

Molby has made measurements of the rotatory power at room and liquid-air temperatures for a few wavelengths. Using these data, the rate of increase of the rotatory power with temperature has been estimated for two wavelengths. Substituting for K and λ_0 in (6) and putting $\chi = 7{\cdot}0 \times 10^{-5}$, $d\rho/dt$ has been theoretically calculated for these wavelengths. These are given in Table IV along with the experimental values.

TABLE IV

λ	$d\rho/dt$ (expt.) (−186° to 20° C.)	$d\rho/dt$ (calc.) $\chi = 7\times10^{-5}$
·5893	..	0·57
·6438	0·18	0·18
·6708	0·12	0·12

Molby has also measured the rotatory power for the red line λ 6438 A.U. at various temperatures ranging from − 188° C. to 20° C. in steps of about 15° C. It is found that the positive temperature coefficient becomes progressively smaller as the temperature of the crystal is lowered.

Proceeding in the same manner as before, χ has been calculated for the different temperatures. The values are given in Table V.

TABLE V

Temp. °C.	$d\rho/dt$	$\chi \times 10^5$
+12·3	0·26	9·9
− 6·5	0·27	10·5
− 32	0·24	9·1
− 55	0·17	6·4
− 79	0·23	8·8
− 98	0·29	11·0
−112	0·19	7·2
−136	0·08	3·2
−155	0·03	1·0
−167	0·05	1·9
−180	0·09	3·4

Because of the difficulty of measurement there are some spurious fluctuations in the experimental values of $d\rho/dt$, but broadly speaking, one can see that χ tends to become very small at the lower temperatures. In fact, many crystals exhibit a similar behaviour, the rate of shift of their characteristic frequencies, as estimated from the thermal variation of the refraction, being found to diminish to negligible values at very low temperatures.

It would be of interest to see how the value of χ calculated above compares with that obtained from the thermal variation of the refractive indices of cinnabar. Values of dn/dt for both the indices are given in the *International Critical Tables* (1930) for a few wavelengths. With these data and the formula (4), χ has been evaluated for the ordinary index in the manner suggested by Ramachandran (1947). It has been assumed that the extreme ultraviolet absorption does not shift with temperature. We then get the expression

$$\frac{dn}{dt} = -\frac{\gamma(n^2-1)}{2n} + \frac{1}{n}\frac{k\lambda^4}{(\lambda^2-\lambda_0^2)^2}\chi_0,$$

where γ is the coefficient of cubical expansion, $k = 0{\cdot}5594$ from (4) and χ_0 and λ_0 have the same significance as before. The value of γ has been estimated from the linear expansion data (*International Critical Tables*) and is found to be equal to $57{\cdot}3 \times 10^{-6}$. Putting $\chi = 10{\cdot}5 \times 10^{-5}$, dn/dt has been calculated for a few wavelengths and has been presented in Table VI.

TABLE VI

λ	$dn/dt \times 10^5$ (expt.) ($-50°$ to $+12°$ C.)	$dn/dt \times 10^5$ (calc.) $\chi = 10{\cdot}5 \times 10^{-5}$
·599	13	12
·6075	9	10
·624	8	7
·644	5	5
·718	2	1

The agreement between calculated and experimental values is quite good. It will be seen that the values of χ as estimated from the temperature coefficients of rotation and refraction are about the same. It should be remarked that the data of $d\rho/dt$ appearing in Table IV are the values at a temperature of about $-80°$, while those of dn/dt in Table VI are given at $-20°$ C. Hence χ is slightly less in the former case.

In conclusion, I express my best thanks to Prof. Sir C. V. Raman for the useful discussions I had with him during the course of this work.

4. SUMMARY

It is shown that a rotatory dispersion formula of the Drude type is inappropriate in the case of cinnabar. On the other hand, a formula of the type $\rho = k\lambda^2/(\lambda^2 - \lambda_0^2)^2$, which has been arrived at from certain theoretical considerations, represents it well. The characteristic wavelength used in this formula also fits the ordinary dispersion curve. By assuming that λ_0 shifts with temperature, the thermal coefficient of the rotatory power has been quantitatively accounted for, the rate of change of λ_0 being found to be about the same value as that estimated from the thermal variation of refraction.

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